THE INCIDENCE AND OUTCOME

OF ACUTE RENAL FAILURE (ARF) IN THE

SURGICAL INTENSIVE CARE UNIT

A dissertation submitted to the TN.Dr.MGR medical University, Tamil Nadu, in partial fulfillment of the rules and regulations for the M.D. branch X (Anaesthesiology)

Examination to be held in February 2007

CERTIFICATE

This is to certify that this dissertation entitled **"THE INCIDENCE AND OUCOME OF ACUTE RENAL FAILURE IN THE SURGICAL INTENSIVE CARE UNIT"** is a bonafide work done by Dr.Vinodh.M.P. in partial fulfillment of the rules and regulations for the M.D. Branch X (Anaesthesiology) examination of the Tamil Nadu , Dr. M.G.R .Medical University , Chennai, to be held in February 2007.

Dr. Nagamani Sen M.D., D.A
Professor,
Department of Anaesthesiology,
Christian Medical College
Vellore. Tamil Nadu

Dr. Manickam Ponniah, M.D., D.A.,
Professor and Head,
Department of Anaesthesiology,
Christian Medical College
Vellore. Tamil Nadu

ACKNOWLEDGEMENTS

I wish to express my deep gratitude to Dr.Nagamani Sen, M.D.,D.A., Professor and Head of the Surgical Intensive Care Unit, and Professor of Anaesthesia, Department of Anaesthesia, Christian Medical College, Vellore, for her valuable guidance and constant encouragement throughout the course of the study.

I am thankful to Dr. Manickam Ponniah, M.D.,D.A.,Professor and head of the Department of Anaesthesia , for his interest and help in the successful completion of the study.

I am extremely thankful to all patients, my colleagues and staff of the Surgical Intensive Care Unit for the cooperation they extended during the course of the study.

I wish to express my deep appreciation to Dr.Antonisamy.Ph.D, Head of the Department of Biostatistics and Mr. Prasanna Samuel, Department of Biostatistics, for their valuable help in the statistical analysis of the study.

CONTENTS

INTRODUCTION

Acute renal failure (ARF) in critically ill patients is associated with a high mortality rate. Several pathophysiologic mechanisms associated with ARF have enhanced our understanding of the disease. ARF can result from alterations in renal perfusion, changes in glomerular filtration and tubular dysfunction. Early intervention and correction of these factors can alter the effects of ARF. Several new potential interventions including renal replacement therapy (RRT) have been developed that can change the course of ARF in the critically ill. Despite improvements in intensive care and dialytic technology, there have not been significant improvements in patient survival over the past few decades. There is no consensus definition of ARF in critically ill patients. Many different definitions have been used in the literature, making comparisons difficult. Timely identification of the severity of ARF using relevant criteria and aggressive intervention remains the key to higher success rates in dealing with these patients. In our study we aim to assess the ability to identify the severity of ARF in the surgical intensive care unit using a new criteria called the RIFLE score (Risk, Injury, Failure, Loss and End stage renal disease), and the effects of early identification of the vulnerable population on the outcome.

AIMS AND OBJECTIVES

- To determine the incidence of Acute Renal Failure in a cohort of patients with risk, injury and failure factors admitted to the Surgical Intensive Care Unit of the Christian Medical College Hospital.

- To assess the mortality in patients who developed acute renal failure.

Review of Literature

I Introduction

II Expanded definition

III Incidence

IV Etiology

- Risk factors
- Causes

    1) Pre renal

    2) Intrinsic

    3) Post Renal

V Pathogenesis

VI Pathophysiology

VII Management

- Diagnosis
- Prevention
- Supportive measures until recovery

VIII Outcome

- Morbidity and mortality
- Long term outcome and quality of life in survivors

I. Introduction

The clinical condition of Acute Renal Failure (ARF) is said to occur in 1% to 25% of critically ill patients depending on the population being studied and the criteria used to define its presence [1,2] . Acute Renal failure characterized by a sudden loss of the ability of the kidneys to excrete wastes, concentrate urine, conserve electrolytes, and maintain fluid balance, is a frequent clinical phenomenon, particularly in the intensive care unit, where it is associated with a mortality of between 50% and 80% [3-6].

Bywaters and Beall described an acute loss of kidney function that occurred in severely injured crush victims during the bombing of London in World War II [7.] Acute tubular necrosis (ATN) was the term used to describe this clinical entity. ARF as a result of ATN may develop in 10% of all patients admitted to the intensive care unit (ICU) and is associated with high morbidity and mortality. Historical sequence of events suggests that early intervention could prevent the occurrence of ARF [7]. Moreover early intervention with fluid resuscitation was shown to prevent the progression from prerenal azotemia to established ARF [7] .

II. Expanded definitions for ARF

The definitions of acute renal failure have varied enormously from one clinical series to another (Table 1). The accuracy of a creatinine clearance measurement is limited, because as glomerular filtration rate (GFR) falls creatinine secretion is increased, and thus the rise in serum creatinine is less[8,9] . Thus creatinine excretion is much greater than the filtered load, resulting in a potentially large overestimation of the GFR (as much

Table 1		
Historical definitions for ARF [18]	Author	Year
> 1 mg% rise in Scr or 20 mg% or 50% rise in BUN	Eisenberg et al	1981
0.5 mg% rise in Scr if baseline <1.9mg% 1 mg% rise in Scr if baseline is 2.0 to 4.9 mg% 1.5 mg% rise in Scr if baseline is >5 mg%	Hou et al	1983
50 % rise in Scr to at least 4 mg%	Parfrey et al	1989
Six graded criteria >0.3 mg% and 20% rise in Scr on day 1,2,or 3 and day 5,6 or 7 0.3 mg% rise on day 1,2 ,3 >20% rise Scr on day 1 or2 2 mg % rise on day 1 or 2 1 mg % rise in Scr on day1 20 mg% or 50%rise in BUN on day 1	Lautin et al	1991
Sudden rise in Scr of 2 mg% with prior normal function Sudden rise in Scr of >50 % with baseline "mild to moderate" CRF with Scr < 3.0 mg% ,Elevation of Scr at admission with normal or increased renal size(except with myeloma or hydronephrosis)	Pascual and Liano	1996
0.5 mg% rise in Scr to at least 2 mg%, or admission Scr >2 mg% with no history of renal disease	Kurnik et al	1998
> 50% rise in Scr in absence of volume responsive pre renal status,> 1 mg% rise in Scr with known renal insufficiency	Fiaccadori et al	1999
SCr >3 mg% with baseline <1.8 mg% or acute decrease in creatinine clearance of <25% following surgery, trauma, hypotension or sepsis	Hirschberg et al	1999
Table 1 contd. 0.9 mg % rise if baseline Scr <2.0 mg% to at least 2 mg% 1.5 mg % rise in Scr if baseline Scr > 2.0 mg%	Behrend and Miller	1999
0.5 mg % rise in Scr to at least 2.0 mg%or admission Scr >2.0 mg% with no past history of renal disease	Obialo et al	2002

as a twofold difference)[8]. However, for clinical purposes it is important to determine whether renal function is stable or getting worse or better. This can usually be determined by monitoring serum creatinine alone [10].

The degree to which serum creatinine changes from baseline will reflect the change in GFR. Serum creatinine is readily and easily measured and it is specific for renal function, while urea (or blood urea nitrogen) is a nonspecific marker of renal function, making it a poor marker relative to creatinine. Urine output is far less specific except when it is severely decreased or absent. Severe ARF can exist despite normal urine output (i.e. non oliguric) but changes in urine output can occur long before biochemical changes are apparent.

The ability to predict hospital mortality in 2 ARF-specific severity-of-illness scoring methods, the Risk, Injury, Failure, Loss, End-Stage Renal Disease (RIFLE) score and the other criteria were compared. Maximum RIFLE score for the first 3 days in the ICU was found to be an independent predictor of hospital mortality along with admission sequential organ failure assessment (SOFA) score [11].

III. Incidence of ARF

Hou *et al* reported an ARF incidence estimate of 4.9% [12]. Shusterman *et al* conducted a similar study identifying ARF in 1.9% of hospitalized patients [13]. A follow-up study recently published by Hou and colleagues [14] showed an increase in incidence to 7% with a similar spectrum of risk factors. In intensive care units, again a few studies have mentioned the incidence of acute renal failure. Clermont *et al* [4] have described an

Study	Incidence	Study limitations
Hou *et al*.[12]	4.9%	Wide range of creatinine values allowed (under inclusion criteria (upto 5 mg%)
Nash *et al* [14]	7.2%	Broad definition for ARF as the above
Kaufman *et al* [19]	0.9%	Broad definition for ARF
Liaño *et al*.[20]	0.37%.	The ICD-9-CM (sensitivity of only 19.2%) was used for coding.
Liangos *et al* [21]	1.9%.	The ICD-9-CM again was the coding used
Chertow *et al* [1]	13%	Small elevations in serum creatinine were associated with increased mortality risk.
Schusterman *et al* [13]	1.9%	Study was restricted to a single center
Ballal *et al* [16]	13%	No specific limitation

Table-2 : Annual incidence of ARF in different clinical studies

incidence of 17% of admissions with ARF in their study of which half had ARF at the time of admission and the other half following their admission into ICU.

Singhri *et al* in their study in a tertiary care referral center quote an incidence of ARF amongst all patients undergoing treatment in their hospital of 5-7% [15]. In a tertiary level hospital in a developing country like India incidence of ARF in hospitalized patients is between 1- 5% and in the ICU is about 10-30% [16] . A prospective study in a tertiary care hospital in lucknow, India showed that 17% of cases of ARF were critically ill [17]. The incidence of ARF in various studies are given in tables 2 and 3.

IV. The Etiology of Acute Renal Failure

Risk factors

Drugs : Aminoglycosides are well-recognized nephrotoxins that are often used and the incidence of ARF with aminoglycoside therapy ranges from 5 to 25%. The accumulation of drug in renal tubular epithelial cells appears to be an important pathophysiologic mechanism but alterations in renal plasma flow may also occur. Renal hypoperfusion predisposes to aminoglycoside nephrotoxicity. Prins *et al* [29] found that compared with conventional thrice-daily dosing, once-daily amino glycoside dosing resulted in a marked reduction in the incidence of ARF (defined as an increase in serum creatinine of 0.5 mg/dl) from 24% to only 5% .Two recent meta-analyses subsequently demonstrated a non significant trend toward less nephrotoxicity with relative risks of ARF of 0.74 to 0.87. Equal clinical and microbiologic efficacy has been consistently demonstrated. [30, 31]

Study	Clinical Circumstance	Incidence
Hoste et al [22] Schrier et al [23]	Sepsis Moderate sepsis Severe sepsis Septic shock	15-30% 19% 23% 51%
Hoste et al [22]	Increasing age	16.2%
Liano et al [6]	Male predominance	65%
Thakar et al [24]	predominance of ARF in females after cardiac surgery	68.5%
Gul et al [25]	Patients with ventilator associated pneumonia (VAP)	38%
Belbi et al [26]	Burns	11%
Hoste et al [27]	Pre ecclampsia	25%
Frederic S. Bongard et al [2]	Immunocompromised Seropositive for HIV	50%

Table 3 : Incidence of Acute renal failure in special circumstances.

The anti fungal agent amphotericin B causes significant renal dysfunction. In a randomized trial of liposomal amphotericin B versus conventional amphotericin B in patients with sustained neutropenic fever, ARF (defined as either a doubling of serum creatinine or a level greater than 3 mg/dl) occurred in only 12% of patients treated with liposomal amphotericin B versus 26% in the conventional group [32].

Colloids : Currently, three hypotheses are presented to explain the mechanisms of ARF associated with colloid use, *i.e.*, accumulation of a low-mol weight fraction in the renal tubules, induction of osmotic nephrosis-like lesions (vacuolization of the proximal tubular cells) and hyperoncotic renal failure [33]. The intratubular accumulation, hyperviscosity, and precipitation of low-mol wt fractions of dextran in the presence of decreased transglomerular filtrate seem to be specific for dextran solutions [35]. The induction of osmotic nephrosis-like lesions has been reported for dextran as well as for gelatin and Hydroxy ethyl starch (HES) [33]. Although these lesions were initially considered to be responsible for the deterioration in renal function, the significance of vacuolization of the proximal tubular cells remains incompletely understood because these alterations were also observed without accompanying ARF. The hypothesis of hyperoncotic renal failure which was first described by Moran and Kapsner [34] seems to explain the pathophysiologic considerations. The GFR depends on the imbalance between positive hydrostatic pressure (renal perfusion pressure) and oncotic forces at the membrane of the glomeruli. In cases of low renal perfusion pressure in the glomerular arterioles, an increase in the colloid oncotic pressure (COP) attributable to an accumulation of unfilterable, osmotically active

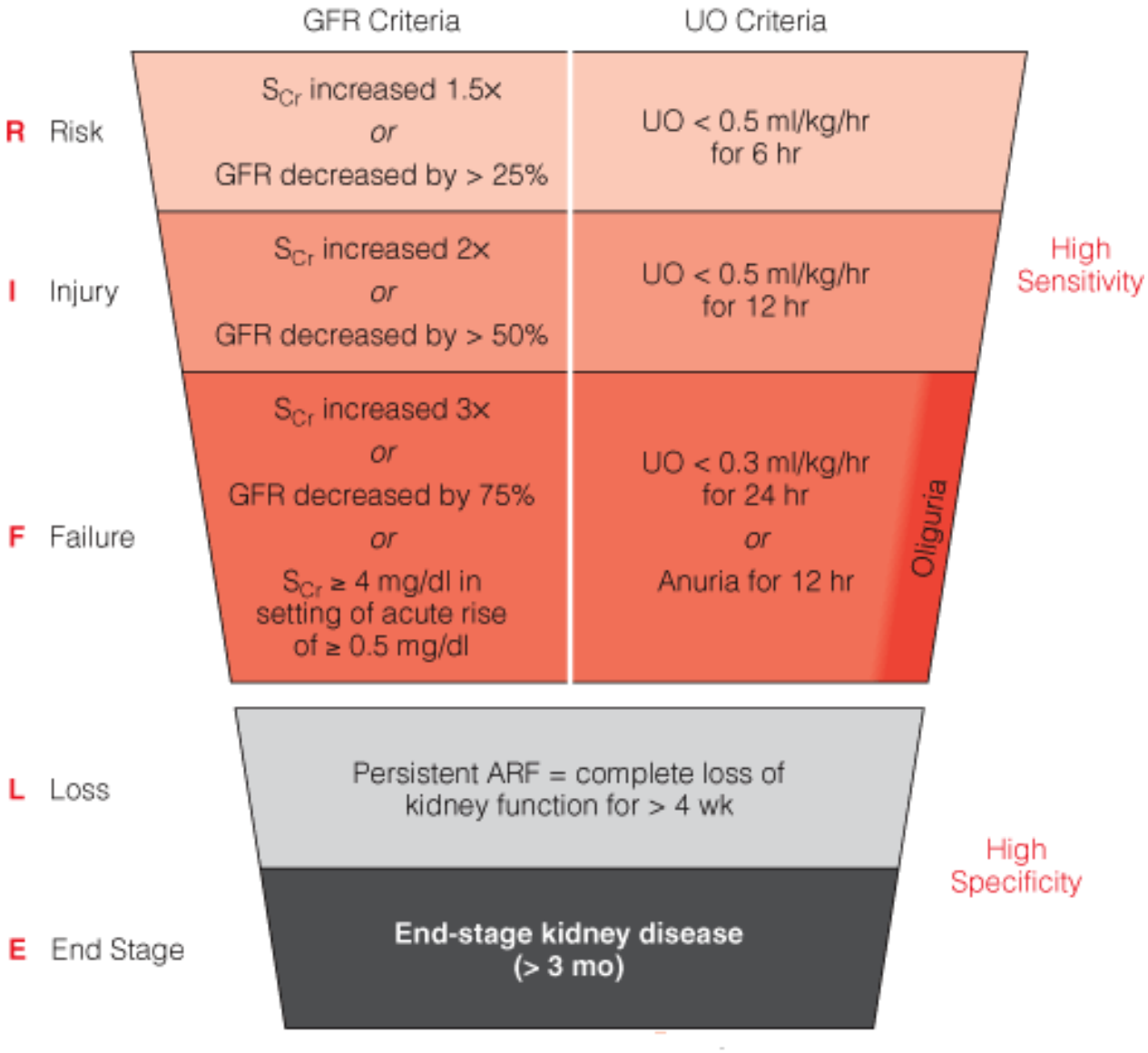


Figure 1 The RIFLE classification for Renal Failure (2004) [120]

substances in the plasma, induces reduction or cessation of glomerular filtration. The back-leakage of filtrate across ischemic or otherwise damaged tubular epithelium additionally reduces renal excretory function [33] .

In patients with severe sepsis, the use of higher substitution hydroxyethylstarch (HES) was associated with a significantly higher risk of ARF than gelatin [36] . Voluven interferes significantly less than HAES-steril with coagulation factor VIII levels and partial thromboplastin time [37] .

Though high concentrations of the colloid (10% HES) or repeated administration of HES with a high *in vivo* mol wt increase the risk of ARF, hemodynamic instability, obstructive vascular disease, dehydration, and preexisting renal insufficiency seem to have greater predisposing effects on the development of ARF than does the type of colloid administered [33]. HES solutions with a low *in vivo* mol wt, such as HES 200/0.5, did not increase the risk for ARF even when used in large amounts intraoperatively or postoperatively [38-40].

Contrast agents : Radiographic contrast agents are thought to involve renal vasoconstriction; adenosine may play an important role in mediating the response [41] .

NSAIDs: In patients with diminished renal perfusion, NSAIDs can precipitate prerenal azotemia [42] .

Rhabdomyolysis and myoglobinuria: Volume depletion and an acidic urine pH predispose to the development of ARF, whereas volume repletion, high urine flow rates, and an alkaline pH are protective[41]. In a retrospective study of 20 patients with

myoglobinuria, all of whom had oliguria and azotemia despite the correction of volume deficits, the administration of mannitol and sodium bicarbonate was associated with increases in urinary output and prompt resolution of renal failure [43]. Ward et al [44] through a multivariate analysis revealed that the presence of dehydration on presentation was an independent risk factor for ARF.

There are no randomized, controlled clinical trials and many of the uncontrolled trials of prophylaxis against myoglobinuric renal failure have involved small numbers of patients. Patients with traumatic rhabdomyolysis in whom the requirement for crystalloid may be quite large, should undergo prompt and aggressive volume resuscitation.. Although the efficacy of bicarbonate and mannitol administration remains unproven, animal studies support their use, and in the absence of complicating factors such as severe hypokalemia and hypocalcemia, the risk of treatment with these agents in this setting is low [41].

Cirrhosis : Renal failure occurs in the absence of identifiable precipitants such as hypovolemia, infection, or treatment with nephrotoxic drugs. These patients are said to have hepatorenal syndrome (HRS), which is thought to arise as a result of the severe circulatory derangement that accompanies cirrhosis [41].

Causes of Acute Renal Failure

The causes of acute renal failure can be categorized as prerenal, intrinsic, and postrenal. (Table 5)

Prerenal Causes

Pre renal	Vomiting ,Diarrhea,Decreased fluid intake Increased fluid losses,Cardiac failure Liver dysfunction, Septic shock Anaesthesia.
Renal	• Toxins : Aminoglycoside antibiotics, Heme Pigments,Chemotherapeutic agents, Myeloma proteins • Auto immune disorders • Infiltrative diseases (sarcoidosis) • Infectious agents
Post renal	• Malignancy • Prostatic hypertrophy • Neurogenic bladder • Intraluminal causes bilateral renal calculi, papillary necrosis, coagulated blood,fungus, • Extraluminal, such as retroperitoneal fibrosis, tumors. • Intrarenal intratubular obstruction various crystals, uric acid, calcium oxalate, acyclovir,sulfonamide, methotrexate, myeloma light chain

Table 4 : Causes of Acute renal failure

Prerenal azotemia is rapidly reversible if the underlying cause is corrected. Elderly patients are particularly susceptible to prerenal azotemia because of their predisposition to hypovolemia and high prevalence of renal-artery atherosclerotic disease [45] . The combination of angiotensin-converting–enzyme inhibitors and diuretics can cause prerenal azotemia in patients with large-vessel or small-vessel renal vascular disease[46,47]. Among critically ill patients, prerenal azotemia is often due to septic shock, cardiac failure or liver dysfunction. [12]

In surgical patients, prerenal azotemia is a common cause of perioperative and postoperative renal dysfunction. Anesthesia decreases effective blood volume and, when accompanied by a reduction in mean arterial pressure, can lead to a decrease in renal blood flow. A wide spectrum of clinical conditions can result in a generalized or localized reduction in renal blood flow, thus increasing the likelihood of ischemic acute renal failure. The most common condition leading to ischemic acute renal failure is severe and sustained prerenal azotemia.

Intrinsic Causes

Intrinsic renal diseases that result in acute renal failure are categorized according to the primary site of injury: tubules, interstitium, vessels, or glomerulus. Injury to the tubules is most often ischemic or toxin induced. Prerenal azotemia and ischemic tubular necrosis represent a continuum, death of tubular cells. Many clinical conditions can lead to kidney ischemia as a result of either extrarenal or intrarenal factors that compromise renal blood flow. Although most cases of ischemic acute renal failure are reversible if the underlying cause is corrected, irreversible cortical necrosis can occur if the ischemia is severe,

Most common mechanisms of abnormal renal blood supply in acute renal failure

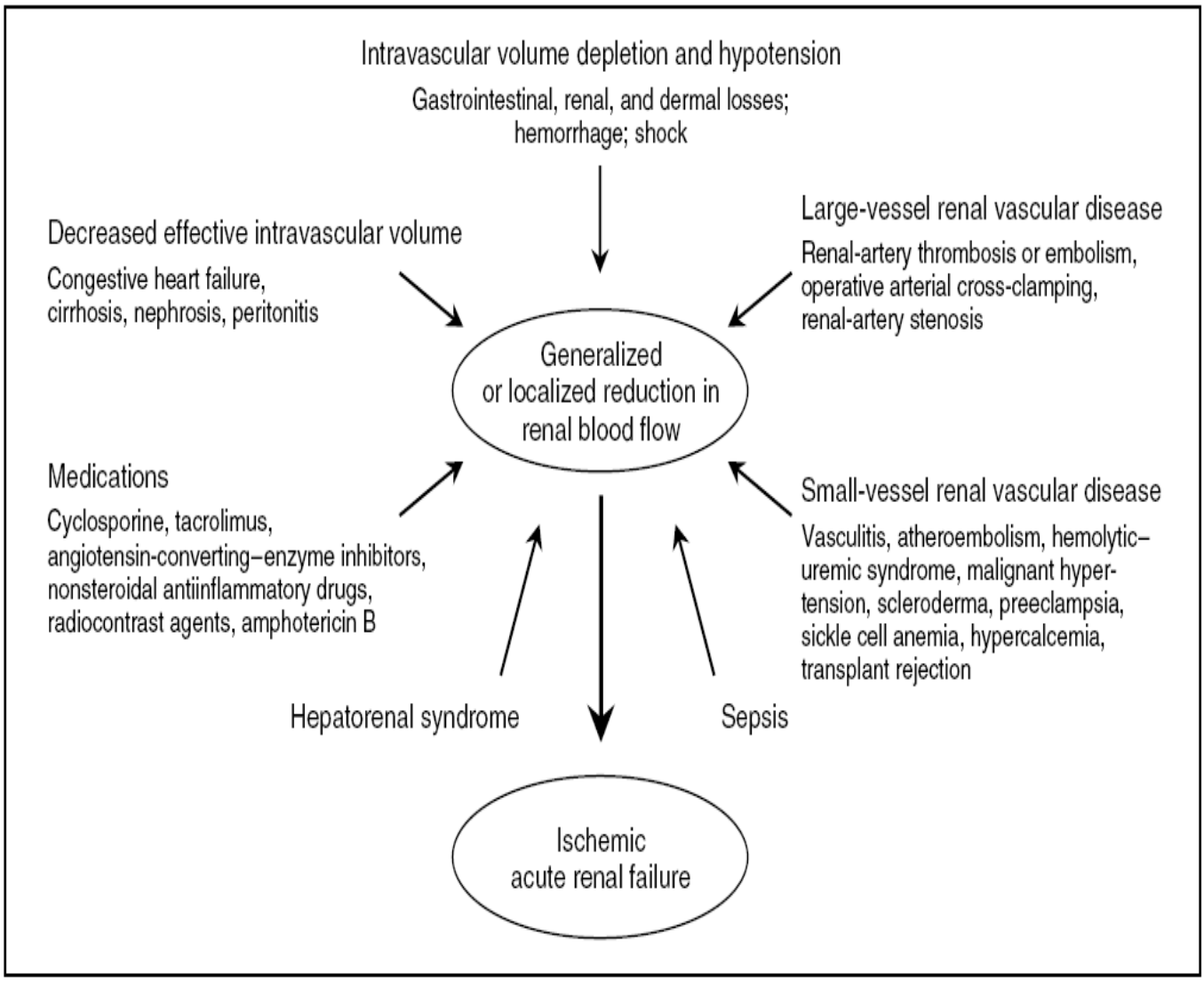


Figure 2

especially if the disease process includes microvascular coagulation such as may occur with obstetrical complications, or the hemolytic–uremic syndrome [48]. Acute renal failure due to acute interstitial nephritis is most often caused by an allergic reaction to a drug [49].

Postrenal Causes

Acute renal failure occurs when both urinary outflow tracts are obstructed or when one tract is obstructed in a patient with a single functional kidney. Postrenal causes are important to rule out quickly, since the potential for recovery of renal function is often inversely related to the duration of obstruction [50].

V Pathogenesis of ARF

Prerenal azotemia and ischemia are common causes of ARF. In addition, toxins that cause tubular necrosis share many pathophysiologic features with ischemic acute renal failure. Vasoconstriction, desquamation of tubular cells, intraluminal tubular obstruction, and transtubular back-leakage of the glomerular filtrate are pathophysiologic mechanisms that have been well characterized [51].

Vascular Factors

Intrarenal vasoconstriction caused by an imbalance between vasoconstrictive and vasodilative factors may result from systemic or local vasoactive agents that act on the small vessels of the kidney. The resulting ischemia can directly alter endothelial-cell function, decreasing the production of and response to vasodilative substances [51].

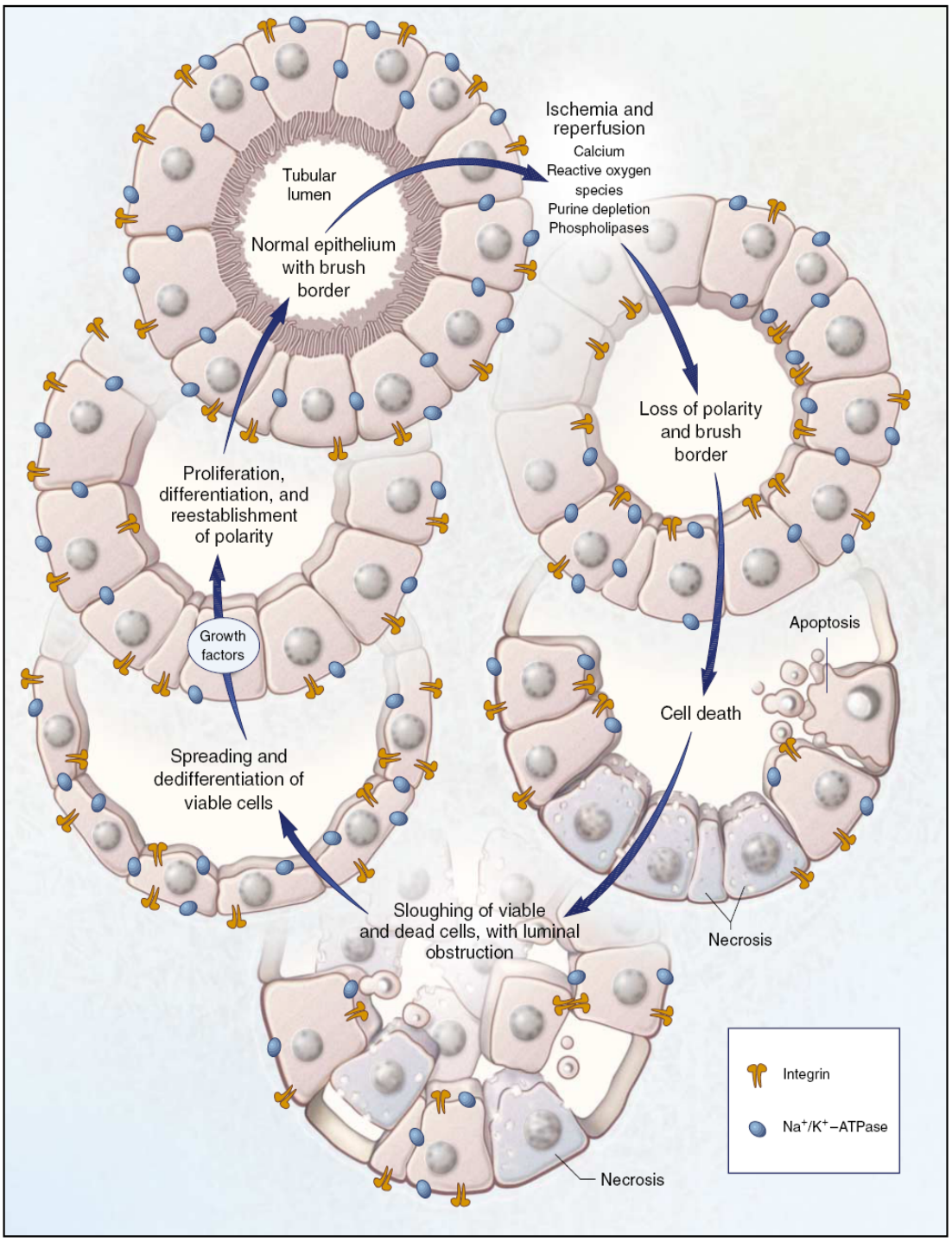


Fig 3: Morphologic changes occurring in the proximal tubule after ischemia and reperfusion

Renal Medullary Hypoxia

Heterogeneity of intra renal blood flow contributes to the pathophysiology of ischemic acute renal failure. An imbalance between the vasodilator nitric oxide and the vasoconstrictor endothelin may also impair medullary blood flow and contribute to tubular-cell damage. In the outer medulla, where tubules have high oxygen requirements, ischemia causes swelling of tubular and endothelial cells as well as adherence of neutrophils to capillaries and venules. These changes lead to vascular congestion and decreased blood flow, tipping the tenuous balance between oxygenation and energy demand [52,53] .

Structural Changes and Tubular-Cell Injury

A hallmark of ischemic and toxic acute renal failure is injury and death of tubular cells. The pathophysiologic events leading to the death of necrotic tubular cells are complex. After ischemia and reperfusion, morphologic changes occur in the proximal tubules, including loss of the brush border, loss of polarity, and redistribution of integrins and Na+/K+–ATPase to the apical surface. Calcium, reactive oxygen species, purine depletion, and phospholipases probably have a role in these changes in morphology and polarity, as well as in the subsequent cell death that occurs as a result of necrosis and apoptosis. There is a sloughing of viable and nonviable cells into the tubular lumen, resulting in the formation of casts and luminal obstruction and contributing to the reduction in the glomerular filtration rate (Fig 3). The severely damaged kidney can completely restore its structure and function. Spreading and dedifferentiation of viable cells occur during recovery from ischemic acute renal failure which duplicates aspects of

normal renal development. A variety of growth factors have been shown to probably contribute to the restoration of a normal tubular epithelium.

Biochemical Changes

Calcium

Depletion of cellular ATP, which accompanies ischemia, leads to an increase in the cytosolic calcium concentration in cells [54]. In addition to its vasoconstrictive effects, calcium can contribute to epithelial-cell toxicity through its ability to activate proteases and phospholipases, break down the cytoskeleton, and interfere with mitochondrial energy metabolism. Although increases in calcium occur soon after hypoxia in experimental systems [54], there remains some controversy about the extent to which increased intracellular calcium causes the ischemic tubular-cell injury.

Reactive oxygen species

Partially reduced species of oxygen can cause marked tissue injury. With the restoration of oxygen after a period of ischemia there is a rapid burst of oxidant formation. The sources of these oxidants in the kidney include cyclooxygenases, mitochondrial electron transport, mixed-function oxidases of the endoplasmic reticulum, the xanthine oxidase system, and neutrophils. The role of reactive oxygen species in ischemic acute renal failure remains in question. Some studies in animals show that antioxidants or scavengers of reactive oxygen species protect against functional tissue damage, whereas other studies do not [55].

Purine depletion

Ischemia leads to the breakdown of ATP and the formation of adenosine, inosine, and hypoxanthine, all of which can leak out of cells, constrict intrarenal arterioles, and contribute to the formation of reactive oxygen species [55]. Although in one study ATP and magnesium protected against ischemic injury in rats [56], other experiments showed that ATP injured oxygenated proximal tubules and was vasoconstrictive [57].

Phospholipases

Phospholipase A2, a family of enzymes that hydrolyze phospholipids to free fatty acids and lysophospholipids can contribute to ischemic cellular injury in various organs [55]. Activated phospholipase A2 can alter the permeability of cell and mitochondrial membranes, disturbing the bioenergetic capacity of the cell. Peroxidation of membrane lipids due to ischemia and reperfusion enhances the susceptibility of membranes to phospholipase A2[58]. In addition, arachidonic acid, a product of phospholipase A2, is converted to eicosanoids that are vasoconstrictive and chemotactic for neutrophils. No specific inhibitors of phospholipase A2 are available for use in humans.

Apoptosis

Pathological evidence of apoptosis has been found in postischemic kidneys in animals [59] and in clinical acute renal failure in humans[55]. Apoptosis seems to be particularly prevalent in post-transplantation acute renal failure, where it coexists with necrosis [60].

Neutrophil chemotaxis

The adherence of neutrophils to the vascular endothelium is an essential step in the extravasation of these cells into ischemic tissue. Chemotaxis of neutrophils is partly due to the activation of the complement cascade, with local formation of C5a. After adherence and chemotaxis, neutrophils release reactive oxygen species, proteases, elastases, myeloperoxidase, and other enzymes that damage the tissue. These substances, together with leukotriene B4 and platelet-activating factor, can both increase vascular permeability and up-regulate the expression of adhesion molecules that promote further inflammation. In models of renal, myocardial, and intestinal ischemia, the depletion of neutrophils, blockade of neutrophil adhesion to the endothelium, and inhibition of the complement system all reduce tissue injury [61-66].

Intercellular adhesion molecule 1 (ICAM-1) on endothelial cells interacts with CD11a/CD18 and CD11b/ CD18 on neutrophils, promoting the adhesion of neutrophils to endothelial cells [61]. The administration of a monoclonal antibody directed against ICAM-1 protects animals from ischemic acute renal failure, even when given two hours after the ischemic event [67]. In addition, mice with a deficiency of ICAM-1 are protected against acute renal failure [65]. Antibodies against ICAM-1 have been administered safely to allograft recipients in a phase 1 trial [68] .

Acute Renal Failure in Transplant Recipients

Ischemic injury to an allograft from a cadaveric donor can lead to delayed graft function, which has been associated with acute rejection and decreased graft survival [69,70]. Extensive local release of cytokines, complement activation, and increased expression of MHC class I and II molecules occur as a result of kidney ischemia. [71,72].

Furthermore, at the site of ischemia, local production of tumor necrosis factor and complement fragments induces the expression of selectins and ICAM-1 on endothelial cells. Preliminary studies with antagonists of platelet-activating factor and antibodies against ICAM-1 suggest that platelet activation and leukocyte–endothelial-cell interactions may be important in early post-transplantation renal failure and rejection in humans[64,68] . In the future, other approaches to decrease ischemic injury and rejection in the allograft may include the use of complement inhibitors, anticytokine agents, or endothelin antagonists [73] .

Pathophysiology of ARF

Direct consequences

Direct consequences are related to the decreased production of erythropoietin and the retention of organic or inorganic wastes that are normally excreted by the kidneys.

Uremic retention

Though well described in chronic renal failure, uremic toxicity may occur irrespective of the levels of urea in the blood . Urea may not cause toxicity on its own. Serum urea is probably a marker for other compounds that may cause toxicity. Uremic toxicity in patients cannot be extrapolated to patients with ARF [74].

Anaemia

Decreased erythropoietin levels or erythropoietin resistance secondary to infection are responsible for decreased bone marrow synthesis of the vital precursors. Uremia induced fragility of the red cell membranes leads to decreased half lives. Uremic coagulopathy leads to increased blood loss.

Direct consequences	Retention of compounds • Organic compounds- uremic toxicity • Inorganic compounds – water and electrolytes Decreased production of metabolites- erythropoietin
Indirect consequences	Side effects of treatment for ARF • Side effects of Drug therapy • Side effects of Renal replacement therapy • Adverse drug reactions

Table 5 : Pathophysiology of ARF

Fluid balance

The BEST (beginning and end supportive therapy) trial for patients showed a use of diuretics for more than 70% of their patients. In many patients an important reason for initiating renal replacement therapy is the onset of volume overload and oliguria. Volume over load has been seen to cause increased complications and in fact a negative impact on the outcome of patients coming for surgery as shown in the beneficial circumstances of improved recovery in the fluid restricted arm, amongst a cohort under going major colorectal surgery [74].

Electrolyte abnormality

Impaired free water clearance cause dilutional hyponatremia in patients with acute renal failure. Hyponatremia results in osmotic imbalances causing swelling up of cells (mainly neurologic) resulting in a wide range of symptoms from headache to coma. The rapidity of onset of hyponatremia is directly related to increased likelihood of symptoms [75]. In addition to conditions which cause a shift of potassium ions from the intracellular compartment, such as acidosis, rhabdomyolysis and hemolysis, the failure to excrete potassium results in an accumulation of potassium ions in the extra cellular compartment [74].

Acid Base Status

When kidney function is decreased there occurs an accumulation of organic and unmeasured ions. There occurs decreased production of bicarbonate by decreased proximal tubular reabsorption and regeneration. Metabolic acidosis is accentuated by decreased buffering capacity secondary to hypoalbuminemia .Non renal etiologies of metabolic acidosis such as lactic acidosis, respiratory acidosis caused by

permissive hypercapnia, ventilation and ketoacidosis seem to compound the effect of mixed disorders [76].

Increased inflammation

The normal inflammatory reaction seems to be dysregulated in acute renal failure and this seems to be the cause of the ensuing multi organ failure in may of the patients admitted in the intensive care unit. Pro inflammatory mediators such as tumor necrosis factor and interleukin 1 beta , 6 and 8 have increased levels in patients with ARF as compared with normal patients or patients with end stage renal failure. The level of interleukin 10 is also increased suggesting an inflammatory anti response .After ischemia, reperfusion of the kidneys causes a dysregulation in the salt and water channels and increased vascular permeability in the lungs leading to interstitial edema [77].

Dysregulation of the lung and water channels has been related to the severity of ARF suggesting that uremia may be responsible. There is considerable evidence to show that ARF is caused at least in part by an inflammatory cascade of events. It has been postulated that this inflammatory response is likely to be the cause of generalized inflammation and organ dysfunction.

The type of acidosis may also seem to affect the degree of inflammation, be it respiratory, metabolic, hyperchloremic or lactic. Hyperchloremic acidosis is more pro inflammatory than lactic acidosis. In vivo acidosis leads to increased nitric oxide levels and lower blood pressure value. A decrease in gut barrier function and an increase in lung and intestinal injury have been documented.

Decreased immunity

Since ARF patients also experience uremia it is possible that these patients also have some degree of immune suppression. Normal leukocyte, neutrophil, and lymphocyte function is affected by acidosis as well as uremic retention compounds like leptin, advanced glycation end products, guanidine and p – cresol. Other factors such as malnutrition, iron overload, anemia and bio incompatibility of dialyser membranes which are commonly associated with chronic uremia may also be seen in the setting of acute renal failure [78].

Cardiovascular changes

Though hypotension and shock are the findings one would commonly tend to see in the setting of acute renal failure, hypertension can also be occasionally seen in patients with volume overload and increased intravascular volume. Volume overload may cause congestive cardiac failure and subsequently hypotension. Intra abdominal hypertension may occur as a result of ascites, retroperitoneal tissue edema and increasing intra abdominal pressures. The resulting compression of the inferior vena cava may result in decreased filling pressures and hence a drop in the cardiac output. Abnormal lung function due to decreased functional residual capacity caused by the upward shift of the diaphragm, may result. Decreased perfusion of the intra abdominal organs and ileus will accompany liver and kidney malfunction.

Moderate hypochloremic acidosis increases nitric oxide levels and inducible nitric oxide synthase leading to lower blood pressure values. Hypotension ands shock are compounded by preexisting co morbidities seen a good number of critically ill patients, such as anemia and coronary artery disease [79].

Pulmonary function

Volume over load may cause pulmonary congestion, pleural effusions or intra abdominal hypertension leading to impaired gas exchange. Dysregulation of the inflammatory cascade and increased vascular permeability may result in interstitial edema. Increased incidence of infections and pneumonia may ensue. Needless to say loss of muscle mass and over sedation may prolong the duration of mechanical ventilation.

Neuromuscular disease

Increased muscle breakdown, and decreased protein metabolism lead to decreased muscle mass. Polyneuropathy though more common in patient with chronic renal failure can also be seen patients with ARF. Difficulty in weaning off from mechanical ventilation may be a consequence of the above.

Infection

Studies show that infections could lead to as much as 40% of the mortality in patients with acute renal failure. Acidosis related insulin resistance and anaerobic glycolysis is associated with decreased immune dysfunction and increased susceptibility to infection. Insulin resistance induced hyperglycemia has been described to be an important risk factor for multi organ dysfunction and death in critically ill patients. Tissue edema may delay wound healing and increases the risk of infections [80].

VII. Management of Acute Renal Failure

Diagnosis

The diagnosis of renal failure using the serum creatinine, and creatinine clearance levels have already been discussed above. A few old as well as new modalities which can help in the diagnosis and classification of ARF.

Fractional excretion of sodium

The Indications for using this modality of investigation include Renal Failure Assessment in prerenal azotemia and acute tubular necrosis . If the FENa is less than <1% it would most likely indicate prerenal azotemia.it would also be consistent with a spot Urine Sodium <30 meq/L . If the FENa >2%: Acute Tubular Necrosis (ATN) could be the diagnosis made and it would be consistent with spot Urine Sodium >30 mEq/L . It is said to have certain disadvantages . FENa is invalidated by diuretics. FENa has to be delayed until 6-8 hours after the last diuretic dose, and can be found to be low despite presence of ATN in certain subsets of patients with ARF (such as with post-ischemic ATN ,use of IV contrast, acute glomerulonephritis and vasculitis) [81].

Urine spot sodium

Urine sodium concentration is used to determine the cause of hyponatremia and help guide therapy. A spot test showing urine sodium concentration of less than 30 mEq/L differentiates patients with hypovolemic hyponatremia from patients with euvolemic hyponatremia. A high urine sodium concentration may be found in

patients with volume depletion secondary to a renal cause of salt wasting (eg, adrenal insufficiency, thiazidediuretic use), metabolic alkalosis or osmotic diuresis (eg, from hyperglycemia). Nephrotic syndrome, congestive heart failure and cirrhosis typically have a low urine sodium concentration unless patients are taking a diuretic, whereas renal failure tends to cause a high urine sodium concentration [82].

Urinary Para Amino Hippuric acid (PAH) clearance, traditionally used as a test of renal plasma flow may grossly underestimate renal plasma flow in those with ARF [83]. Total renal plasma flow measured by alternate techniques, is close to normal during the extension, maintenance, and recovery stages of ischemic renal injury.

Techniques of Measurement of GFR in Patients with ARF

GFR is commonly measured using plasma or renal clearance of marker solutes administered as a bolus or continuous infusion. The reference standard is renal inulin clearance but other solutes commonly used include radioactive (^{125}I-iothalamate, ^{51}Cr-EDTA) or non-radioactive markers (iothalamate, iohexol, polyfructosan). Paramagnetic agents (gadolinium DTPA) are rarely used. GFR can be measured by various methods including the continuous infusion method (IM), the standard clearance method (CM) or the plasma clearance method [84].

Continuous Infusion Method without Urine Collection

This method is not suitable for use in patients with ARF [84] in view of the unstable GFR in these patients.

Standard Clearance Method with Urine Collection

This method lends itself well to estimation of GFR in ARF when hemodynamic changes can be rapid. By collecting urine and plasma at timed intervals, rapid changes in GFR can be detected [84].

Radioactive Markers 51Cr-EDTA and 99m Technetium-diethylene triamine penta acetic acid (99mTc-DTPA) have been used. Plasma clearance showed an excellent correlation with simultaneous GFR measurements performed with a standard ^{125}I-iothalamate clearance technique. Renal function was monitored in patients at risk for ARF during angiography or in the intensive care unit under noninvasive and near real-time conditions. The results indicate that the technique detects rapid changes in renal function with a resolution time of 5 min in patients with normal renal function, and 15 min in patients with severely impaired renal function.

Pitfalls in the measurement of GFR) in ARF

Measurement and estimation of GFR in ARF presents numerous challenges. Serum creatinine concentration alone will provide inaccurate information of estimated GFR when the GFR is rapidly changing or before it reaching an equilibrium value. Urinary clearance of GFR markers may provide better information. Thus, if a bolus of a marker such as inulin was administered intravenously and its urinary clearance measured, an estimate of GFR can be obtained.

The choice of the GFR marker such as inulin, 125-I iothalamate, and others has been validated in patients with stable renal function. Increased transcapillary

hydraulic pressure gradient and tubular dilatation was the predominant cause of persistent renal failure in patients with ischemic transplanted kidneys [86]. Leakage of substances filtered at the glomerulus but which leak back across the tubular epithelium, may underestimate GFR in ARF. Olbricht *et al* [85] measured the permeability to those substances most commonly used for filtration rate determination, such as polyfructosan and inulin, by measuring their recoveries after perfusion through various nephron segments in ischemic and nephrotoxic models of ARF in animals. Distal recovery of polyfructosan and inulin were reduced by a maximum of 11%, and urinary recovery of inulin was reduced by only 15% in kidneys showing severely restricted renal function. Thus the reduction in whole kidney inulin or polyfructosan clearance reflects primarily a reduction in GFR, although there is also a small component of back leak.

CystatinC: It is a cysteine protease inhibitor of low molecular weight and is produced constantly by nucleated cells, is excreted by the glomerulus and thus closely reflects GFR, and may well be a better marker of GFR than creatinine [87].

Magnetic Resonance Imaging in Acute Renal Failure

Recent technical developments in contrast MRI have permitted ultrafast imaging with short acquisition times. Gadolinium-chelates are non-nephrotoxic, freely filtered by the glomerulus, and not reabsorbed or secreted by the tubules [88]and are well suited to assess GFR. Besides detection of urinary tract obstruction or renal parenchymal abnormalities, vascular, especially arterial, morphology is accurately and rapidly assessed from the supra-aortic to the distal peripheral arteries in one diagnostic procedure. This is

of interest, as patients with ARF may also suffer from atherosclerosis or abdominal aortic aneurysms or may present with renal arterial or venous obstruction or occlusion.

The loss of corticomedullary differentiation is a sign of changing differential perfusion to the renal cortex and medulla in ARF. MRI may be valuable to distinguish vascular complications and acute allograft rejection after renal transplantation. Blood oxygenation level-dependent (BOLD) contrast MRI depends on the principle that hemoglobin (because of its iron content) changes its magnetic qualities depending on whether hemoglobin is in the deoxygenated or the oxygenated form. Deoxyhemoglobin shows paramagnetic, oxyhemoglobin diamagnetic effects in the magnetic field. Therefore, deoxyhemoglobin acts as an endogenous contrast agent, and increased deoxyhemoglobin concentration leads to signal attenuation in T2 weighted MR sequences. Because the ratio of deoxyhemoglobin to oxyhemoglobin is related to the pO_2 of blood, which again is thought to be in equilibrium with the surrounding tissue, BOLD MRI can noninvasively estimate tissue pO_2 in humans. BOLD MRI measures intrarenal oxygenation and not perfusion and cannot distinguish between alternating oxygenation induced by changing perfusion or by oxygen consumption [89] .

Prevention of Acute Renal Failure in the Critically Ill

Prerenal azotemia and acute tubular necrosis (ATN) are the most frequent causes of ARF in ICU. Preventive strategies should focus on methods that may augment renal perfusion or reduce renal oxygen consumption.

Low-dose dopamine is known to result in renal artery dilatation, natriuresis, and diuresis. Low-dose dopamine continues to be widely used to protect against ARF and ameliorate established ARF without much benefit. (Table -6)

Fenoldopam is a specific DA-1 receptor agonist. In a study involving fenoldopam (Prospective, double-blind, placebo-controlled trial) continuous infusion of fenoldopam (n = 150) at 0.09 microg x kg x min the incidence of ARF was significantly lower in the fenoldopam group compared with the control group (29 vs. 51 patients; p = .006). The length of intensive care unit stay in surviving patients was significantly lower in the fenoldopam group compared with the control group (10.64 +/- 9.3 vs. 13.4 +/- 14.0; p < .001. Compared with placebo, low-dose fenoldopam resulted in a smaller increase in serum creatinine in septic patients [41].

Osmotic Agents and Diuretics: Mannitol, furosemide and bumetanide have also been used to increase intratubular flow rates. Mannitol and other osmotic agents help preserve transplanted kidneys ex vivo and prevent delayed graft function, which is most often caused by ischemia [91]. Mannitol has been used along with vigorous volume replacement and sodium bicarbonate, for the prevention and treatment of early myoglobinuric acute renal failure [92]. This agent is also used together with adequate hydration in an attempt to prevent the nephrotoxic effects of cisplatin [41].

Although mannitol and furosemide have been shown in animals to help protect the kidney against ischemic injury most studies in humans have failed to demonstrate the effectiveness of these agents in the prevention or treatment of ischemic or toxic acute renal failure [93,94].

Author	Design	Patient population	Outcomes	Dose of dopamine	Conclusion
Swygert et al	Randomized double blind placebo controlled	Liver transplant	Urine output BUN/serum creatinine	3 mcg/kg/min	Inconclusive
Baldwin et al	Prospective Randomized double blind placebo controlled	Abdominal aortic aneurysm Aorto femoral grafting	Serum creatinine/ BUN/ Creatinine clearance	3 mcg/kg/min	No benefit
Kadiera et al	Prospective controlled	Kidney transplant	Graft function 1 week 3 months post surgery	3 mcg/kg/min	Inconclusive
Chertow et al	Randomized placebo controlled	ARF	Dialysis Death	>3mcg/kg/min <3mcg/kg/min	Inconclusive
Bellomo et al	Randomized placebo controlled	ARF in ICU	Serum creatinine	2 mcg/kg/min	No significant improvement
Abiziad et al	Prospective Randomized	CRI undergoing coronary angiography	Serum creatinine Dialysis	2 mcg/kg/min	No improvement

Table – 6: Studies involving Dopamine[41]

Both mannitol and loop diuretics, if administered early in the course of ischemic ARF can convert an oliguric to a nonoliguric state. Although nonoliguric acute renal failure is generally associated with a lower mortality rate, there is little evidence that conversion from an oliguric to a nonoliguric state decreases the mortality rate [41]. Diuretics can be detrimental in acute renal failure induced by radio contrast agents [95-97]. In the setting of cardiovascular surgery diuretics are used to decrease renal oxygen consumption and to prevent the accumulation of intraluminal debris that may cause obstructing casts. Conger found no evidence to support use of prophylactic mannitol in non transplant surgery [98]. In a small study of cardiac surgery patients, prophylactic use of furosemide infused at 0.5 µg/kg/min was associated with significant worsening of renal outcome compared with placebo [97].

Atrial natriuretic peptide (ANP) is a potent diuretic and natriuretic substance. A 48-h infusion of ANP was found to improve renal blood flow and GFR [99]. In a study of 504 critically ill patients with ATN, even though there was no effect of a 24-h infusion of a synthetic ANP, on dialysis-free survival, analysis demonstrated that in patients with oliguria, there was a 27% dialysis-free survival compared with only 8% in the placebo groupIn non oliguric patients dialysis-free survival was 48% versus 59% in the control group [100]. Another study of 222 oliguric patients with ATN treated with ANP for 24 h found a nonsignificant trend toward improvement in 14-d and 21-d dialysis-free survival, but 60-d mortality rates were similar [101].

Volume expansion and vaso active drugs

In a nonrandomized study of 56 patients with sepsis and hypotension, the addition of nor adrenaline to low-dose dopamine was associated with an increase in the mean creatinine clearance from 75 to 102 ml/min [102].Nor adrenaline infusions in septic animals have been shown to induce increased renal blood flow in animals [103]. Gattinoni L et al in their multicenter study, therapy (volume expansion and vasoactive drugs) aimed at achieving supranormal values for the cardiac index or normal values for the mixed venous oxygen saturation had no effect on the frequency or severity of renal dysfunction [104]. No randomized control trial has compared fluids with no intervention, but fluids resuscitation does have benefit especially in situations such as traumatic rhabdomyolysis.

Free radical scavenging:

Free oxygen radical injury is believed to be an important component of SIRS, and selenium-dependent glutathione peroxidase is one of the main free radical scavenging systems [41]. The role of selenium deficiency and replacement was explored in a randomized trial of 42 ICU patients diagnosed with SIRS whose mean selenium levels were approximately 40 to 50% of the normal values [105]. In the group assigned to receive repletion with intravenous sodium selenite, the mean creatinine concentration was significantly lower and only 3 of the 21 patients required continuous venovenous hemodialysis, compared with 9 of the 21 control patients. Mortality was also reduced in the selenium repleted group particularly in those with the highest Acute Physiology and Chronic Health Evaluation III (APACHE III) scores (36% versus 89%). No side effects of the selenium repletion regimen were recognized.

Corticosteroids may hasten the recovery of renal function during acute interstitial nephritis [41], but their role remains controversial because controlled studies are lacking and corticosteroids may be contraindicated in patients with underlying infection.

Ischemia reperfusion renal injury and N Acetyl Cysteine (NAC)

The exact mechanism by which NAC may prevent renal contrast induced nephropathy (RCIN) is unknown, although antioxidant and vasodilatory effects likely play a key role. NAC directly scavenges oxygen free radicals and also serves as a precursor of glutathione, itself a natural antioxidant. In addition NAC increases the concentrations of both nitric oxide, a potent but short acting vasodilator, and S-nitrosothiol which has more prolonged vasodilatory effects [106].

The beneficial effects of NAC on the outer medullary circulation may be dependent not only on free radical scavenging but also on NO potentiation, both of them promoting vasodilatation and preventing leukocyte activation and leukocyte-endothelial adhesion and, ultimately, precluding the endothelial dysfunction associated with ischemia-reperfusion processes [107].

Liver disease

Hepato renal syndrome (HRS) is a major cause of mortality in the critically ill. Sort et al randomized patients to determine the effect of albumin and renal impairment, defined by the study investigators as a greater than 50% rise in blood urea nitrogen or creatinine. Renal impairment occurred in only 10% of the patients receiving

albumin compared to 33% in the other group. The administration of albumin was also associated with a significant reduction in mortality [108].

Several recent studies have examined the effect of splanchnic vasoconstrictors like ornipressin in patients with HRS. 3 days of low-dose vasopressin led to significant increases in urinary flow but GFR actually decreased [109,110].

Supportive measures till recovery

Renal Replacement Therapy (RRT) and its Adequacy

Intermittent HD remains the dominant mode of RRT all over the world, used in more than two-thirds of cases in recent surveys.

Indications

- Features of uremia
- Hyperkalemia refractory to medical management;
- Volume overload unresponsive to fluid restriction and diuretics;
- Metabolic acidosis that is severe or accompanied by volume overload,
- Precluding adequate bicarbonate therapy;
- Certain dialyzable intoxications (e.g., lithium, toxic alcohols, salicylate,digoxin)
- Hypocalcemia, hyperphosphatemia, or hypercalcemia
- anuric ARF unresponsive to acute interventions

Classification of renal replacement therapies

Renal replacement therapies currently available include intermittent HD, peritoneal dialysis, and various forms of CRRT. CRRT techniques are classified according to the driving force for blood flow (spontaneous/arteriovenous or pumped/ venovenous techniques) and the predominant solute transport process employed.

Solutes that are small enough may be transported with water(solvent drug) across a semipermeable membrane by convection. Ultrafiltration occurs when water is driven across a membrane by a pressure gradient. Slow continuous ultrafiltration (SCUF), with ultrafiltration rates of 200 ml/h does not cause significant solute clearance. When hemofiltration is performed for uremia therapy however, increased hourly ultrafiltration rates of 1-2 L/h are customary and urea clearance by continuous arteriovenous (CAVH) or venovenous (CVVH) hemofiltration is substantial. During hemofiltration, administration of "replacement fluid" containing buffer (bicarbonate or lactate) and various electrolytes (sodium, potassium, calcium, magnesium, phosphorus) prevents iatrogenic acidosis and electrolyte depletion and further lowers the plasma concentration of uremic solutes by hemodilution, augmenting the effect of simple transmembrane urea clearance. The most complex form of CRRT combines convective and diffusive solute transport during continuous hemodiafiltration (CAVHDF or CVVHDF).

The precise timing of RRT initiation is usually a matter of clinical judgment. This pattern of practice is based primarily on early experience suggesting that uremic bleeding diathesis and hemorrhage were reduced when hemodialysis was initiated before the BUN exceeded 100 mg/dl [111].

Intermittent versus continuous renal replacement therapy

CRRT is most frequently used in patients who are hemodynamically intolerant of intermittent HD usually because of sepsis or severe cardiac dysfunction. Control of azotemia with venovenous CRRT is possibly superior to daily intermittent HD in large or hypercatabolic patients [112].

Anti coagulation in CRRT

CRRT without anticoagulation may be successful in some coagulopathic patients such as those with end-stage liver disease. In many septic patients with thrombocytopenia and elevated prothrombin time/partial thromboplastin time (PT/PTT) due to diffuse intravascular coagulation (DIC), increased filter clotting is the rule if no anticoagulation is used. In newly postoperative patients and others with contraindications to systemic anticoagulation, regional anticoagulation of the hemofilter alone is preferred.

Biocompatibility

Biocompatible membranes are more expensive but data does not suggest any clinical adverse effect of their use in severe ARF, which is likely to continue unless proven ineffective or harmful by a major prospective trial.

Dose of renal replacement therapy

Clearance of urea, a low molecular weight nitrogenous waste product is the most commonly studied marker of adequate uremic detoxification by HD. The term Kt/V is a unitless measure of HD dose (based on urea removal): K is the urea clearance of

Therapeutic goal	Hemodynamic condition	Preferred renal replacement therapy
Urea clearance	Stable Unstable	Intermittent hemodialysis CRRT Convection-CAVH,CVVH Diffusion – CAVHD,CVVHD Both- CAVDHF,CVVHDF
Severe hyper kalemia	Stable /unstable	Intermittent hemodialysis
Severe metabolic acidosis	Stable Unstable	Intermittent hemodialysis CRRT
Severe hyper phosphatemia	Stable/unstable	CRRT
Fluid removal	Stable Unstable	Intermittent isolated ultrafiltration Slow continous ultrafiltration or peritoneal dialysis

Table 7: Indications for different modes of RRT

the dialysis membrane used (ml/min), t is the duration of dialysis (min), and V is the volume of distribution of urea in the patient (ml). Thus, Kt/V is a measure of the volume of plasma cleared of urea during an HD session (Kt) divided by the urea distribution volume (V, assumed to be total body water: 0.5-0.6 L/kg), and larger Kt/V values signify greater HD dose. Kt/V measurements of delivered dialysis dose are usually calculated using the ratio of postdialysis to predialysis BUN and a nomogram [113].

Dialysis Outcomes Quality Initiative recommendations defined a Kt/V of 1.2 as the minimum acceptable dialysis dose in chronic HD patients. No such dosing guidelines have been established for the ARF population.

Results of a prospective, observational studies show that 68% of ARF treatments failed to deliver the minimum dialysis dose recommended for maintenance HD of renal failure patients and for 49% of treatments a minimally adequate dialysis dose was not even prescribed. Failure to adjust dialysis dose and/or achieve adequate dialysis delivery in larger patients was a major source of treatment failure [113].

In a study by Schiffl daily intermittent HD was associated with a markedly lower mortality than alternate day therapy (21 versus 47%, $p < 0.025$) in a group of 72 ICU patients with ARF [114]. Simple interventions should include use of anticoagulation whenever possible (to minimize loss of dialyzer surface area), replacement of catheters with suboptimal blood flow rates, and most importantly, prescription of an increased dialysis dose for larger patients.

VIII Outcome

Mortality in acute renal failure

Reported ICU mortality rates in patients with ARF vary between 20 and 70%. Although some studies say that only pronounced impairment of renal function was associated with significant morbidity and mortality, other studies have shown that slight increases on serum creatinine >0.5mg% in post operative patients have been associated with increased mortality [115]. As far as change over the last few decades of mortality in patients with acute renal failure few studies have reported a decline in rates while using similar criteria. McCarthy et al [116] in their retrospective comparison of 71 consecutive ICU patients with ARF during two decades showed a significantly improved rate of hospital survival (52% versus 32%) and 1-year survival (30% versus 21%). The mean total APACHE II score was the same in both study periods.

The results of various mortality studies are as given in table 8. Limitations of these mortality studies the should be noted that although use of ICD-9-CM codes for identification of ARF has been shown to be valid by a previous study [117] sensitivity was low (15%), suggesting that ARF figures that are recorded is likely underreported. A recent study indicated that approximately 80% of patients with biochemical criteria for ARF were not identified by ICD-9-CM code [19]. If these findings are applicable to the general population, then the magnitude of underestimations in this study could be up to five- or six-fold.

Several recent studies have shown two fold higher mortality rates between patients who had ARF and required RRT as against those who had ARF but did not

Study	Type of study	Mortality rate/circumstance	Year
Hou and colleagues [18]	Prospective	25%	1979
Mcarthy et al [116]	Retrospective	52%	1977
Sushrut et al [133]	Retrospective	40.4%	1988
Mcarthy et al [116]	Retrospective	32%	1992
Liano et al [6]	Prospective	45% 65%- subset requiring dialysis	1996
Brivet et al [128]	Prospective	58%	1996
Ralph et al[128]	Prospective	68%- Intermittent hemodialysis 75%-CVVHD	1996
Hou and colleagues [12]	Prospective	19%	1996
Schwilk et al	Prospective	12% -one failing organ system 38% with two OSF, 72% with three OSF, 90% with four OSF 100% with five OSF	1997
Lombardi et al[128]	Retrospective		1998
Mangano et al[134]	Prospective	63% post myocardial revascularization ARF	1998
Mendonca et al[2]	Prospective	42%	2000
Clermont et al [4]	Prospective	57% 75% - subset requiring dialysis	2002
Mehta et al [131]	Retrospective	51.5%	2002
Mehta et al [131]	Retrospective	53%- with use of diuretics	2002
Sushrut et al[133]	Retrospective	20%	2002
Hoste et al [22]	Retrospective	56.7%- with sepsis	2003
Schrier et al [23]	Prospective	70% - with sepsis	2004
Uchino et al [123]	Prospective	60.3%	2005
Liangos et al [21]	Retrospective	22.3%	2006

Table 8: Mortality rates compared from literature[128]

require RRT. The difference was four fold when a critically ill population without ARF was compared with those who required RRT [115]. An important finding of prognostic relevance is that ARF in the ICU is associated highly with the development of multi organ failure.

A study by the Madrid group [20] which has assessed ARF in the above 80 age group showed that the relative risk for mortality in patients aged more than 80 years was 1.09 [95%CI 0.86,1.36 (P = .562)], and in those aged 65 to 79 it was 0.99 [95%CI 0.83,1.18 (P = .954)] compared with patients aged less than 65 years.

Patients with "community-acquired ARF" (i.e., patients in whom ARF was given as the cause for hospital admission) had a lower death rate than those with hospital-acquired ARF [19].

Long term outcome and quality of life in ICU survivors

The long term survival of patients who after having been critically ill and recovered has been reported to be far more encouraging than the in hospital survival rates provided by most studies. In patients who have survived an episode of renal failure the need for post recovery renal replacement therapy has been quoted to be as high as 30%. In one particular study [118] the 6 month survival rate of patients who survived to hospital discharge was approximately 69% and the five year survival rate was 50%. Seventy seven percent of the patients reported good to excellent health status in the above study. Another prospective study revealed six month survival rates of 73% [119]. Literature on quality of life after therapy for ARF say that the health related quality of life (HRQL) may not be predictable from data available at the time of dialysis initiation in the above

study. In retrospect, surviving patients agree with the decision to accept dialysis, even when their HRQL is poor.

In conclusion it is doubtful that we will ever have an epidemiologic surveillance system for ARF comparable to that provided for other infectious or multisystem disorders. Development of a rapid and sustained decrease in GFR, urine output, increase in serum creatinine from the baseline values and /or all the three parameters can be used as a definition for ARF. Current understanding of the epidemiology of ARF as per the available studies adds to the growing evidence that Acute Renal Failure is a major public health burden, taking its toll in morbidity, mortality, and cost, and justifies the call for additional research support to ultimately provide more effective preventive and therapeutic interventions.

MATERIALS AND METHODS

The design of the study was a unicenter observational prospective cohort study. There was no intervention. The duration of the study was a fixed six month period from February 2006 to July 2006 (6 months).

Study population

This study was conducted on all patients >14 years admitted to the surgical intensive care unit, fulfilling any one of the inclusion criteria for acute renal failure. The inclusion criteria that was used for this study is the RIFLE criteria for classifying Renal failure[120]. It is as follows.

Category	GFR Criteria	Urine Output (UO) Criteria
Risk	Increased creatinine x1.5 or GFR decrease > 25%	UO < 0.5ml/kg/h x 6 hr
Injury	Increased creatinine x2 or GFR decrease > 50%	UO < 0.5ml/kg/h x 12 hr
Failure	Increase creatinine x3 or GFR decrease > 75%	UO < 0.3ml/kg/h x 24 hr or Anuria x 12 hrs

Patients were excluded from the study if

a) Age was less than 14 years.

b) Loss or End stage renal disease as defined by RIFLE.

Loss	Persistent ARF = complete loss of kidney function > 4 weeks
ESKD	End Stage Kidney Disease (> 3 months)

Sample size :

As per the statisticians advice a defined period of study was chosen before the onset of study. This period was chosen as six months. All patients admitted under the surgical intensive care unit of this tertiary referral hospital would be screened with the RIFLE criteria and subsequently be included in the study.

Patients fulfilling the criteria on admission as well as patients developing acute renal failure during the course of treatment for other illnesses in surgical ICU were included in the study. The day of admission into the study was considered the first day. All patients were included in the study based on the serum creatinine or the urine output components of the RIFLE criteria. Base line creatinine values for patients with no previous records and no history of preexisting renal disease were estimated using the simplified Modification of diet in renal disease (MDRD) formula. (appendix 1).

Setting: The study was done in the surgical intensive are unit of a multi specialty tertiary care referral hospital. This ICU receives patients from all surgical specialties except cardiothoracic, pediatric and neurosurgical units.

Data collection

Data collection included assessment of severity of illness by calculation of Acute Physiology and Chronic Health Evaluation (APACHE II) score and Sequential Organ Failure Assessment (SOFA) score at admission (Appendix 2,4,5and 6). The data collection also included daily values for serum creatinine, urine output, highest values for lactate and random blood sugar.

There was no randomization of treatment options for the purpose of this study. All management decisions were made as per existing ICU protocol. The indication for RRT was decided in consultation with our team of nephrologists. Patients with ARF were screened for their diagnosis at the time of inclusion in to the study. If the diagnosis was changed during the course of the patient stay in surgical intensive care unit, the one thought to be leading to acute renal failure was considered to be the etiology.

Definitions for sepsis, polytrauma , cardiovascular dysfunction, pulmonary dysfunction , hematological failure and hepatic failure are as per literary guidelines (appendix 7).

Statistical analysis

The SPSS 11.5 (Statistical package for social sciences Inc. Chicago, IL) was used. Continuous data are presented as mean and (standard deviations) and were analyzed with the T test. Comparisons between groups were done using analysis of variance test for numerical values and chi square test for comparing the proportions. An analysis of factors affecting the mortality was done with the above tests. The significant factors which were identified were then subjected to a logistic regression analysis with mortality as the dependant variable. Continuous variables chosen for the logistic regression were then categorized. The odds ratio for acute physiological parameters in the first 24 hours of

ICU admission and causes of ICU admission were studied. In view of the smaller sample size logistic regression analysis was performed on fewer variables. The Calibration of the results of the logistic regression were assessed by goodness of fit from Hosmer lemeshow. The Hosmer Lemeshow test compared model performance (observed versus expected) across the deciles of risk to test whether the model is biased (i.e performs differentially at the extremes of risk. A non significant value for this test suggests an absence of such bias.

Receiver operating characteristic (ROC) curve is a graphical representation of the relationship between the sensitivity and the specificity of a particular test. The area under the curve (AUC) represents the overall accuracy of the test. The larger the area the better is the test. The ROC curve was used to evaluate the APACHE II and the SOFA scores in this population.

All p values less than 0.05 were considered significant in this study.

RESULTS

Incidence of ARF

During the six month study period 422 patients were admitted to the surgical intensive care unit. Of these patients 97 met the RIFLE criteria for acute renal failure. The calculated incidence of ARF is 22.7%.

Demographic pattern of ARF

Of the 97 patients diagnosed to have ARF, the distribution of patients across the deciles of age was a normal distribution, with a bulk of the patients falling in the 30 to 69 age group (Table–1). With respect to sex of the patient (Table-2), males had higher incidence 73.2% vs. 26.8%.

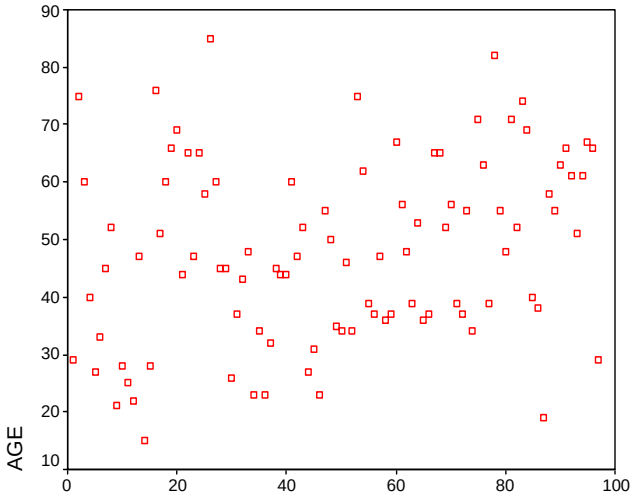
Classification of ARF

In this study, 47% of the patients with ARF belonged to the risk category, 31% of the patients belonged to the injury category and 22 % belonged to the failure category. (Table-3).

Etiology of ARF

The leading cause of ARF in the study cohort was sepsis. 55 of the 97 patients were diagnosed with sepsis. The next most common cause of ARF was polytrauma(10%). ARF following post arrest sequelae was the etiology in 10% of the

Table 1 Demographic pattern in the study population



Scatter diagram showing a good age distribution of the study population

Table 2

	Frequency	Percent
Male	71	73.2
Female	26	26.8
Total	97	100.0

Gender distribution

Inclusion criteria	Frequency	Percent
Risk	45	47
Injury	32	31
Failure	22	22
Total	97	100

Table 3 : Frequency of acute renal failure based on the inclusion criteria

patients. Hepato renal syndrome and hemorrhagic shock caused ARF in 6 and 4 % of the patients respectively.(Table 4)

Mortality in patients with ARF

Of the 97 patients admitted with ARF the mortality rate was 47%(n=46). The leading cause of mortality was sepsis (Table 4). The case fatality rate for sepsis was 62%. The combination of sepsis with ARF is associated with a high mortality in our study. Sepsis was found to be a significant cause of mortality ($p<0.01$). Polytrauma was found to be a significant cause of mortality ($p<0.05$).

Survival in the three groups

Of the 51 survivors in the study, 31 patients belonged to the risk group. 13 patients belonged to the injury group and only 7 belonged to the failure group (Table 5). Among the non survivors the number of patients falling under the risk group was 14, under the injury group was 17, and the failure group was 15.

Prognostic screening

The risk, injury and failure groups were compared with each using the APACHE II score, the APACHE predicted mortality, the APACHE adjusted mortality and the SOFA score (Table 6). .

Table 4: Etiology of Acute Renal Failure and outcome

Etiology	Frequency	Percent	Mortality	Case fatality	P value
Sepsis	55	56.7	34/55	62%	<0.01
Polytrauma	10	10.3	1/10	10%	<0.05
Crush syndrome	4	4.1	3/4	75%	NS
Hepato renal syndrome	6	6.2	2/6	33%	NS
Acute cardio-respiratory failure	10	11	5/10	50%	NS
Major surgery	6	6.2	0/6	0%	NS
Obstructive renal failure	1	1.0	0/1	0%	NS
Renal parenchymal causes	1	1.0	0/1	0%	NS
Hemorrhagic shock	4	4.1	1/4	25%	NS
Total	97	100.0	46/97	47%	NS

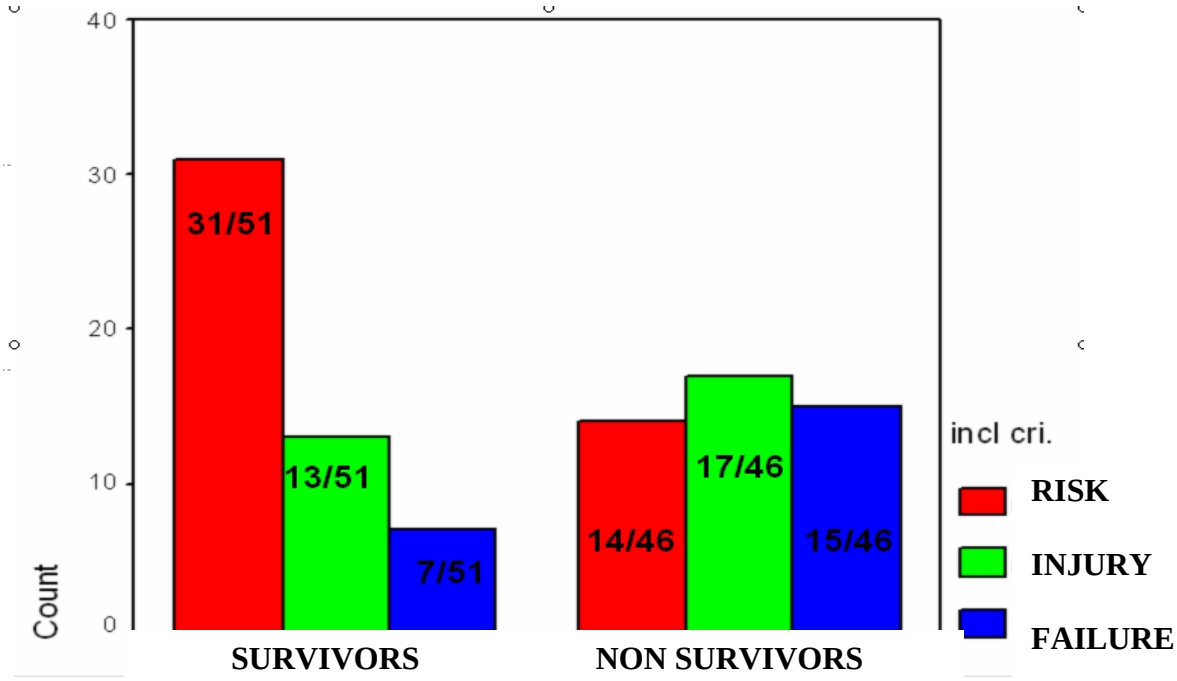


Table: 5 Inclusion Criteria Vs Outcome

APACHE II and the SOFA score showed a clear demarcation between the three groups. All mean values for the three groups were found to be lower for the risk and subsequently higher for the injury and failure groups. Analysis of variance for these factors was significant statistically ($p<0.001$).

When these prognostic scores were applied to the survivors and non survivors we found significance between them for the APACHE and SOFA scores ($p<0.001$). (Table 6A).

The mean age, number of days in ICU and the duration of mechanical ventilation was higher in the injury group as compared to the risk and failure groups. Statistical significance was lacking for the above factors (Table 6). Between the survivors and the non survivors there was a rise in the mean age, duration of ventilation and the duration of

Table 6: Prognostic screening for patients with Acute Renal Failure based on inclusion criteria

Inclusion criteria		Age (years)	ICU days	Mech. vent days	APACHE II	APACHE expected mortality (%)	APACHE adjusted mortality (%)	SOFA at admission
Risk (n=45)	Mean (SD)	45.27 (15.9)	4.51 (4.12)	3.84 (4.21)	16.73 (6.261)	28.20 (17.43)	30.28 (21.87)	6.71 (3.1)
Injury (n=30)	Mean (SD)	52.43 (15.50)	5.77 (4.84)	5.23 (4.65)	21.0 (7.174)	41.58 (22.32)	47.01 (26.31)	7.4 (2.97)
Failure (n=22)	Mean (SD)	47.0 (15.75)	4.59 (3.81)	4.64 (3.76)	24.64 (3.995)	52.77 (12.24)	65.31 (11.59)	11.4 (3.13)
P value		0.156	0.430	0.378	<0.001	<0.001	<0.001	<0.001

Table 6 A : Prognostic screening for patients based on the outcome

Outcome		Age	ICU days	Mech. ventilation days	APACHE II	APACHE expected mortality (%)	APACHE adjusted mortality	SOFA admission
Survivors (n=51)	Mean SD	43.96 (16.26)	3.47 (3.28)	3.84 (4.21)	15.57 (4.993)	24.74 (13.118)	26.29 (17.974)	6.63 (3.09)
Non surv. (n=46)	Mean SD	52.26 (14.49)	5.54 (4.94)	5.23 (4.65)	24.65 (5.372)	52.51 (17.152)	62.37 (18.282)	10.3 (2.89)
P		0.34	0.41	0.016	0.00	0.00	0.00	0.00

stay in the ICU . There was significance between these two groups for mean duration of mechanical ventilation also (p=0.016).. (Table 6A)

Physiological and biochemical variables:

The lowest values for mean arterial pressures (p=0.002), lowest value for pH(p=0.040), and the highest value for serum creatinine(p=<0.001) (Table 7) were significantly different across the three groups. Similar trends are observed for urine output. The mean value of 24 hourly urine output in the failure group was significantly lower(p<0.001). There was no significance between the risk, injury and failure groups for central venous pressures, arterial lactate, bilirubin and random blood sugar on admission. (Table 7)

Values for mean arterial pressure and central venous pressures on admission were found to be lower in the non survivors, possibly indicating lower filling pressures and perfusion. Mean values for pH were also considerably lower for the non survivors (7.16) as compared to the survivors (7.29). (Table 7A)

There is statistical significance between the survivors and non survivors for values for mean arterial pressures (p=0.00), pH (p<0.001), 24 hourly urine output (p=0.00) and random blood sugar levels(p=0.001).There is no significance for admission creatinine, arterial lactate, bilirubin and central venous pressures between survivors and non survivors.

Table 7: Physiological and biochemical variables for the three groups

Inclusion criteria		MAP (mm of hg)	CVP (cm of water)	pH	Creat mgm%	Blood Sugar (mg%)	1st day urine output(l/day)
Risk (n=45)	Mean (SD)	71.67 (16.37)	7.11 (3.45)	7.254 (0.040)	1.6 (0.25)	170.6 (72.50)	1.496 (0.586)
Injury (n=30)	Mean (SD)	63.47 (16.84)	7.40 (5.17)	7.239 (0.118)	2.4 (0.67)	162.5 (51.36)	1.062 (0.67)
Failure (n=22)	Mean (SD)	57.09 (13.56)	8.11 (5.35)	7.180 (0.127)	3.5 (1.75)	179 (63.07)	0.765 (0.424)
P value		0.002	0.977	0.040	0.00	0.657	0.00

Table 7A: : Physiological and biochemical variables and outcome

Outcome variable		MAP Adm (mm of hg)	CVP Adm (cm of water)	pH adm	Creat adm	Blood Sugar Adm (mg%)	Bilirubin values	Lactate levels	1st day urine output (litres)
Survivors (n=51)	Mean (SD)	71.88 (15.5)	7.35 (5.3)	7.2922 (.09)	2.147 (1.17)	150.80 (66.63)	2.300 (4.71)	2.1 (1.1)	1.556 (.5424)
Non survivors (n=46)	Mean (SD)	59.11 (15.7)	6.74 (4.3)	7.1663 (.092)	2.457 (1.16)	191.41 (54.3)	2.207 (3.0)	2.7 (2.10)	0.770 (0.4776)
P value		0.00	0.54	<0.001	0.196	0.001	0.909	0.14	0.00

Outcome in terms of mortality is statistically significant between survivors and non survivors for the following

- presence of cardiovascular failure ($p<0.001$),
- respiratory failure ($p=0.003$),
- hematological failure ($p<0.001$),
- and presence of systemic infection at admission ($p=0.006$).
- presence of diabetes mellitus ($p=0.046$).

Emergency or elective nature of the surgery did not significantly affect mortality in this study.

Intervention ;

The five variables in this data include use of diuretics, use of the drug N Acetyl cysteine, need for renal replacement therapy(RRT), use of ionotropes and need for mechanical ventilation.

Across all three groups we noticed a uniform pattern of increased usage of diuretics among the non survivors (Table 8). In this cohort 16 patients required RRT of whom 9 were in the failure group. The need for mechanical ventilation was also found to increase as we proceeded from the risk to the failure groups. There was statistical significance between the groups for use of diuretics and RRT. There was no significance for mechanical ventilation between the three groups.

Logistic regression analysis for predictors of mortality was done with parameters and variables found to be significant by the earlier analysis. High blood sugar values >190 mg% (OR 8.58, 2.0-33.2, P value 0.003) and use of diuretics (OR 5.20, CI 1.6- 23.3, P value 0.031) were found to associated with mortality. Hosmer and

Table 8: Intervention provided for the different groups

Inclusion criteria			Diur etics	Iono tropes	Use of NAC	RRT	Mech. vent .
Risk	Survivors	n =31	8	18	7	0	23
	Non survivors	n =14	10	14	4	1	12
Injury	Survivors	n=13	6	7	4	1	11
	Non survivors	n=17	15	17	8	5	15
Failure	Survivors	n=7	5	5	4	2	5
	Non survivors	n=15	13	15	7	7	15
	P value		< 0.01	0.20	0.10	0.001	NS

Table 8A: Intervention provided versus outcome

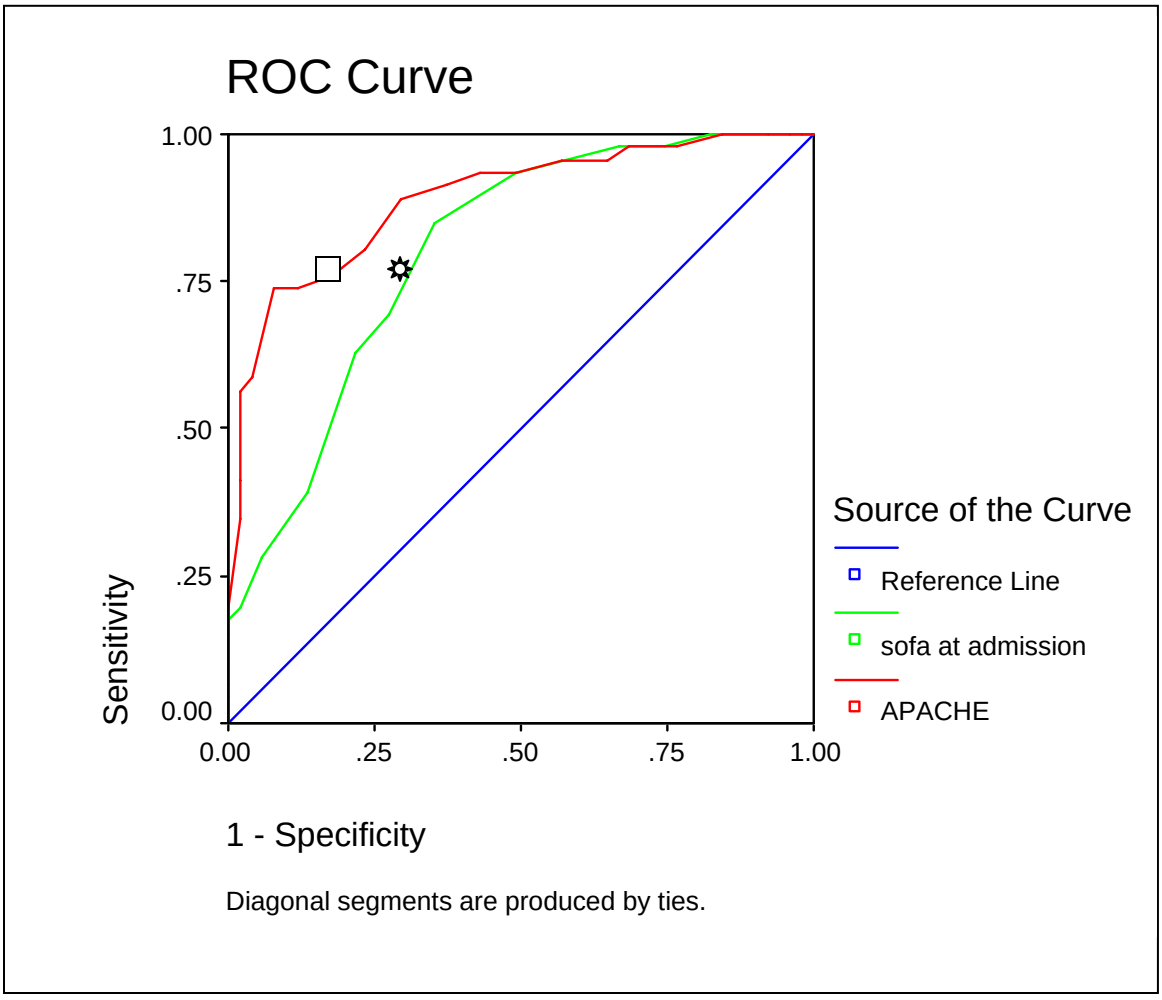
Intervention	survivors	Non survivors	p value
Use of diuretics	30/51	27/46	<0.001
Use of NAC	15/51	19/46	0.220
Use of ionotropes	30/51	46/46	<0.001
Mechanical ventilation	39/51	46/46	0.001
Emerg/ Elect surgery	35/12	38/6	0.281
Need for RRT	3/51	13/46	0.003

lemeshow for goodness of fit test showed a p value of 0.604 with an over all percentage of 77.3%.

All 46 of the non survivors required ionotropes and mechanical ventilation.(Table 8A) Of the 16 patients in the whole study who required dialysis, 13 were non survivors. There is an increases use of diuretics among the non survivors (27/46). The use of diuretics, ionotropes, need for RRT, mechanical ventilation was significantly higher in the non survivors .

We studied the efficacy of the APACHE II and SOFA scores in the study population with the help of an receiver operating characteristic curve (ROC) curve. The ROC curve gives an estimate of the sensitivity and specificity of the test.

At an APACHE II score of 19.5 the test was seen to show a sensitivity of 80% and a specifity of 78%. For SOFA at a value of 8.5 the test was 70%sensitve and 70%specific.



The area under the curve(AUC) for the APACHE 0.890+/- 0.033 p value 0.000

The area under the curve(AUC) SOFA 0.801+/- 0.044 p value 0.000

FIGURE 4

DISCUSSION

In the critically ill population prevalence reported for ARF is in the range of 3% to 25%[2,6,22,115]. The greatest prevalence of ARF (24%) in the critically ill was quoted by Mendonca [2] et al, with renal failure due to surgical or trauma related illness accounting for one fourth the cases. Our study was done only in the surgical intensive care unit and the prevalence was found to be 22%.

Prospective studies[11] involving the RIFLE criteria show an incidence of ARF of 52% of patients.. The proportion of distribution of patients under the risk, injury and the failure groups was – 49%,29% and 22% (Ahlstrom et al[11]), and– 32%, 30.6% and 23% (Obaseif et al [122]). Our study done in the SICU shows an incidence of 22%. The proportion of patients falling into the groups risk, injury and failure was 47%, 31% and 22% respectively.

ARF is found to be more common among the males. Studies by Mehta et al[18], Sural et al[17], Abosaif et al[122] and Hoste et al[22] quote percentages of 71%, 70%, 67% and 66% respectively, in favor of the males. In our study also we found that the incidence was higher amongst the males (73% versus 27%), but with no statistical significance for mortality.

Uchino et al[123] and Mendonca et al[2] have found that increasing age was found to be significantly associated with mortality in patients with ARF. In our study there was no significant relation between age , incidence of ARF, and mortality. This could be because the bulk (table 1) of the patients who were admitted in this study were

between the 30 to 65 age group and the numbers above 65 were not significant enough to be compared. This is similar to findings of other studies[122,22,17,18].

The APACHE II scoring has been found to be reliable and highly indicative of mortality rates. Mehta et al[18] others [11,122,22] all quote a higher APACHE score for patients with increasing severity of acute renal failure.

In our study the mean values for APACHE II in the risk group was 16, for the injury group it was 21, and for the failure group it was 24 (Table 6). Ahlstrom et al[11] in their study quoted values of 16, 18 and 22 as the values for the respective groups. Abosaif [122] et al gave scores of 20, 22 and 26 for the mean values in the three groups respectively..

On comparison of the prognostic factors for mortality the APACHE II score with its predicted rates and adjusted rates was very discriminatory (Table 6A). The APACHE adjusted mortality rate was quite useful in this study given the fact that severity of the precipitating illness was given due importance while considering the outcome.

The SOFA score has been used by Mendonca et al [2] and the SAPS II score was used by Abosaif et al, and they too have found an important association in terms of mortality and higher admission scores. Flavio et al [124] in their prospective study showed that initial SOFA scores of 11 or more was indicative of 80%mortality prediction. This correlated well with the failure group and the non survivors in our study (Table 6 and 6A). ROC curves for the APACHE and SOFA scores for predicting mortality showed values of 19.5 and 8.5 respectively(fig.4).

The most common cause of ARF in this cohort of patients was found to be sepsis. Many studies reported on acute renal failure with a focus on sepsis. Hoste et al [22]

found that the incidence of ARF in patients with sepsis was 16.2%. Rangel et al[125] found an incidence of 19%, Brun et al [126] found an incidence of 21%. Schrier et al [23] found that the incidence of ARF increased to 23% and 51% with culture positive sepsis and septic shock respectively. Mortality rates with ARF complicating sepsis are between 50-70%[127]. Our study showed an incidence of sepsis with ARF of 56% and a fatality rate of 62%.

In a large multicentric study done by Metnitz et al [128] ARF due to polytrauma was seen in 11.7% of all critically ill patients. This study however included medical and surgical patients. Mendonca et al [2] in their study said that 9% of the ARF population was admitted following trauma. In our study polytrauma and crush syndrome were found to be the cause of ARF in 10% and 4%of the patients respectively.

Arabi et al [129] have shown an incidence of ARF in 44 % of critically ill patients with cirrhosis. None of the patients who developed hepato renal syndrome (HRS) in our study were thought to be cirrhotic. Two patients had jaundice complicating pregnancy, with the other four having liver failure due to cholecystitis or malignancy. The study was done in a surgical ICU and hence HRS following cirrhosis may not be present.

Ten percent of patients developed ARF following cardio respiratory arrest. Mattana et al [130] showed that ARF in patients after cardio respiratory arrest has been shown to be associated with a high mortality of 93%. The mortality rate in our study in this subgroup is 50%. The other causes of ARF in our study were major surgery 6%, obstructive renal failure 1%, intrinsic causes 1%, and hemorrhagic shock 4%. These were not associated with mortality significantly.

The duration of stay in ICU was similar in all three groups and was not found to significantly affect outcome (Table6).

Factors leading to the outcome (etiology, clinical and biochemical parameters, and patient management.) in terms of mortality were analyzed by logistic regression. Physiological and biochemical parameters recoded on the first day varied significantly between the risk, injury and failure groups and were predictive of mortality following ARF. These results compare well with those of Hoste et al , Mehta et al and Abosaif et al. Through logistic regression we found that high random blood sugar levels at admission were associated with increased mortality.

Significance was found between the survivors and the non survivors for diuretics ($p<0.001$), ionotropes ($p<0.001$), mechanical ventilation ($p=0.001$), and need for RRT ($p=0.003$. The need for ionotropes, mechanical ventilation and RRT have been shown to be significantly associated with mortality by Uchino et al[123], and Lamiere and Hoste et al [22] . The sicker the patient the more was the use of ionotropes, mechanical ventilation and RRT.

Logistic regression analysis showed that diuretic use was significantly associated with adverse outcomes in ARF. This may be due to a direct deleterious effect of diuretic agents as suggested by Pascual [131] and Mehta, and Lamiere et al [132],or a delay in the institution of RRT. Data from a randomized, blinded clinical trial are not available as of now. More trials are needed to prove its benefit in ARF.

Need for RRT was more in the non survivor(13 out of 46, $p=0.003$) and the failure groups(9 out of 16, $p=0.001$) (Tables 8 and 8A). N Acetyl cysteine was used

based on individual clinicians judgment and was not found to alter outcome. A randomized, control trial is necessary to prove usefulness.

Despite the fact that renal-replacement therapy has been available for decades, many patients have preexisting conditions that predispose them to acute renal failure and to concomitant extrarenal complications that cause multiorgan failure. Although there is a consensus that the need for RRT and the delivered dose of hemodialysis is related to morbidity and mortality, there is no consensus on the appropriate dose in patients with ARF. Conflicting data are available regarding the above[114]. The hypothesis that increasing use of RRT, and increasing the intensity of the delivered dose of hemodialysis in critically ill patients with acute renal failure reduces the rate of uremic complications and improves the outcome is logical, yet remains unproved, since it is based on scarce and conflicting data.

CONCLUSIONS

This study identifies and describes the differences in clinical profile and outcome of patients diagnosed as Risk, Injury, or Failure under the RIFLE scoring for ARF. We found that ARF formed part of the clinical profile in 22% patients admitted in the surgical ICU over a period of six months. Mortality was 47% in those with ARF. Higher APACHE II scores, prolonged ventilation, lower mean arterial pressures at admission, lower arterial pH, lower urine output, and higher random blood sugars levels on admission were associated with higher mortality. The above results show that the RIFLE scoring was quite accurate with regard to identifying the sicker patients among the study population.

We conclude that

1. The RIFLE score is a good assessment of the incidence of ARF in the critically ill population. Each subsequent stage of ARF showed greater mortality than the previous stage.

2. The admission APACHE II and the admission SOFA score were equally good in the predicting the outcome of patients with ARF .

3. Sepsis was associated with the highest incidence of ARF. Cardiovascular, respiratory and hematological system failure at admission, presence of systemic infection at admission, use of diuretics and ionotropes, need for renal replacement therapy, and mechanical ventilation were found to be significantly associated with adverse outcome in ARF.

4. Early institution of RRT could help in improving patients in the injury and failure groups.

5. By using the RIFLE score the early recognition of the risk group is possible and intervention could prevent risk from progressing to failure.

6. Further randomized studies are needed to prove the influence of factors such as diuretics, RRT and Nacetyl cysteine .

.

BIBLIOGRAPHY

1. Chertow GM, Levy EM, Hammermeister KE, Grover F, Daley J: Independent association between acute renal failure and mortality following cardiac surgery JAMA 1998, 104:343-348.
2. De Mendonca A, Vincent JL, Suter PM, Moreno R, Dearden NM, Antonelli M, Takala J, Sprung C, Cantraine F: Acute renal failure in the ICU: risk factors and outcome evaluation by SOFA score. Intensive Care Med 2000, 26:915-921.
3. DuBose TD Jr, Warnock DG, Mehta RL, Bonventre JV, Hammerman MR, Molitoris BA, Paller MS, Siegel NJ, Scherbenske J, Striker GE: Acute renal failure in the 21st century: Recommendations for management and outcomes assessment. Am J Kidney Dis 1997;29: 793–799.
4. Clermont G, Acker CG, Angus DC, Sirio CA, Pinsky MR, Johnson JP: Renal failure in the ICU: Comparison of the impact of acute renal failure and end-stage renal disease on ICU outcomes. Kidney Int 2002;62: 986–996.
5. Metcalfe W, Simpson M, Khan IH, Prescott GJ, Simpson K, Smith WC, MacLeod AM: Acute renal failure requiring renal replacement therapy: Incidence and outcome. Q J Med 2002 95: 579–583.
6. Liaño F, Junco E, Pascual J, Madero R, Verde E: The spectrum of acute renal failure in the intensive care unit compared with that seen in other settings. The Madrid Acute Renal Failure Study Group. Kidney Int 1998 66: S16–S24.
7. Bywaters, E.G., and Beall, D. Crush injuries with impairment of renal function. Br. Med. J. 1**:** 1941. .:427-432.

8. Doolan PD, Alpen EL, Theil GB: A clinical appraisal of the plasma concentration and endogenous clearance of creatinine Am J Med 1962, 32:65-72.
9. Erley CM, Bader BD, Berger ED, Vochazer A, Jorzik JJ, Dietz K, Risler T: Plasma clearance of iodine contrast media as a measure of glomerular filtration rate in critically ill patients. Crit Care Med 2001, 29:1544-1550.
10. Kim KE, Onesti G, Ramirez O: Creatinine clearance in renal disease. A reappraisal. BMJ 1969, 14:11-19.
11. Ahlstrom A, Kuitnnen A, Comparison of 2 acute renal failure severity scores to general scoring systems in the critically ill..Intensive Care Unit, Am J Kid Dis; 2006,88(2);262-268.
12. Hou SH, Bushinsky DA, Wish JB, Cohen JJ, Harrington JT: Hospital-acquired renal insufficiency : A prospective study. Am J Med 1983;74: 243–248.
13. Shusterman N, Strom BL, Murray TG, Morrison G, West SL, Maislin G: Risk factors and outcome of hospital-acquired acute renal failure. Clinical epidemiologic study. Am J Med 1987;83: 65–71.
14. Nash K, Hafeez A, Hou S: Hospital-acquired renal insufficiency. Am J Kidney Dis 2002;39: 930–936.
15. Murray S;ARF Review ; JAMA;2003;289;747-751.
16. Ballal S, S. Kishore Babu . Renal Replacement Therapy in The Intensive Care Unit,ISCCM. www.isccm.org/journals/april2002/journal6.htm
17. SuralS Acute renal failure in an intensive care unit in India –prognostic factors and outcome, Journal of Nephrology 1999:12:390-394.

18. Mehta R, Chertow G: Acute renal failure definitions and classification: Time for a change?: J Am Soc Nephrol 2003; 14, 2178 – 2187.
19. Kaufman J, Dhakal M, Patel B, Hamburger R: Community-acquired acute renal failure. Am J Kidney Dis 1991;17: 191–198.
20. Liaño F, Pascual J: Epidemiology of acute renal failure: A prospective, multicenter, community-based study. Madrid Acute Renal Failure Study Group. Kidney Int ;199650: 811–818.
21. Liangos O, Wald R, O'Bell J, Price L, Pereira B, Jaber B: Epidemiology and outcomes of acute renal failure in hospitalized patients: A national survey. Clin J Am Soc Nephrol 2006;1: 43–51.
22. Hoste EAJ, Lameire NH, Vanholder RC, Benoit DD, Decruyenaere JM, Colardyn FA: Acute renal failure in patients with sepsis in a surgical ICU: Predictive factors, incidence, comorbidity, and outcome. J Am Soc Nephrol 2003;14 : 1022 –1030.
23. Robert W. Schrier, M.D., and Wei Wang, M.D.. Acute Renal Failure and Sepsis NEJM 2004 july 8 ; 351:159-169.
24. Thakar CV, Liangos O, Yared JP, Nelson D, Piedmonte MR, Hariachar S, Paganini: ARF after open-heart surgery: Influence of gender and race. Am J Kidney Dis 2003;41 : 742 –751.
25. Gul G, Demir N, Incidence and risk factors for the development of acute renal failure in patients with ventilator-associated pneumonia ; Nephrology ;june 2006 Volume 11 issue 3 ;159 -165.
26. Belba M, Belba G ; Acute renal failure in severe burns. Conclusions after analyses of deaths during 1998 . Annals of Burns and Fire Disasters 2000- vol. XIII - n. 2 - June .

27. Eric A.J. Hoste , Norbert H. Lameire , Raymond C. Vanholder , Dominique D. Benoit*, Johan M.A. Decruyenaere and Francis A. Colardyn Intensive Care Unit and Renal Unit, Ghent University Hospital, Gent, Belgium.Acute renal failure during eclampsia: incidence risks factors and outcome in intensive care unit. Ren Fail. 2004 May;26(3):215-21.
28. Frederic S. Bongard, Darryl Y. Sue ; Current Critical Care Diagnosis & Treatment.
29. Prins JM, Buller HR, Kuijper EJ, Tange RA, Speelman P. Once versus thrice daily gentamicin in patients with serious infections . Lancet 1993; 341: 335-339 .
30. Hatala R, Dinh T, Cook DJ. Once-daily aminoglycoside dosing in immunocompetent adults: a meta-analysis. Ann Intern Med 1996; 124: 717-725 .
31. Barza M, Ioannidis JP, Cappelleri JC, Lau J. Single or multiple daily doses of aminoglycosides: a meta-analysis. Br Med J 1996; 312: 338-345.
32. Walsh TJ, Finberg RW, Arndt C, Hiemenz J, Schwartz C, Bodensteiner D, Pappas P, Seibel N, Greenberg RN, Dummer S, *et al* . Liposomal amphotericin B for empirical therapy in patients with persistent fever and neutropenia. National Institute of Allergy and Infectious Diseases Mycoses Study. N Engl J Med 1999; 340: 764-771.
33. Baron JF: Adverse effects of colloids on renal function. In: Yearbook of Intensive Care and Emergency Medicine, edited by Vincent J-L, Berlin, Springer, 2000, pp486 -493.
34. Moran M, Kapsner C: Acute renal failure associated with elevated plasma oncotic pressure. N Engl J Med; 1987;317 : 150-153.

35. Mailloux L, Swartz CD, Capizzi R, Kim KE, Onesti G, Ramirez O, Brest AN: Acute renal failure after administration of low-molecular weight dextran. N Engl J Med 1967;277:1113 -1118.
36. Schortgen F, Lacherade JC, Bruneel F, Cattaneo I, Hemery F, Lemaire F, Brochard L. Effects of hydroxyethylstarch and gelatin on renal function in severe sepsis: a multicentre randomized study. Lancet 2001; 357: 911-916.
37. Olivier Langeron, Voluven, a Lower Substituted Novel Hydroxyethyl Starch (HES 130/0.4), Causes Fewer Effects on Coagulation in Major Orthopedic Surgery than HES 200/0.5 Anesth Analg 2001;92:855-862.
38. Godet G, Fleron MH, Vicaut E, Zubicki A, Bertrand M, Riou B, Kieffer E, Coriat P: Risk factors for acute postoperative renal failure in thoracic or thoracoabdominal aortic surgery: A prospective study. Anesth Analg 1997;85:1227 -1232.
39. Vogt NH, Bothner U, Lerch G, Lindner KH, Georgieff M: Large-dose administration of 6% hydroxyethyl starch 200/0.5 for total hip arthroplasty: Plasma homeostasis, hemostasis, and renal function compared to use of 5% human albumin. Anesth Analg 1996 ;83:262 -268.
40. Kumle B, Boldt J, Piper S, Schmidt C, Suttner S, Salopek S: The influence of different intravascular volume replacement regimens on renal function in the elderly. Anesth Analg 1999; 89 : 1124-1130.
41. Harold M, Block C, Prevention of acute renal failure in the critically ill. Am J Resp Med Crit Care 2002.; vol 165,320-324.

42. Shankel SW, Johnson DC, Clark PS, Shankel TL, O'Neil WM Jr. Acute renal failure and glomerulopathy caused by non steroidal anti-inflammatory drugs. Arch Intern Med 1992;152:986-990.
43. Eneas JF, Schoenfeld PY, Humphreys MH. The effect of infusion of mannitol-sodium bicarbonate on the clinical course of myoglobinuria. Arch Intern Med 1979; 139: 801-805.
44. Ward MM. Factors predictive of acute renal failure in rhabdomyolysis. Arch Intern Med 1988; 148: 1553-1557.
45. Pascual J, Orofino L, Liano F, Marcen R, Orte L, Ortuno J: Incidence and prognosis of acute renal failure in older patients. J Am Geriatr Soc 1990;38 : 25 –30.
46. Corwin HL, Teplick RS, Schreiber MJ, Fang LS, Bonventre JV, Coggins CH. Prediction of outcome in acute renal failure. Am J Nephrol 1987;7:8-12.
47. Davidman M, Olson P, Kohen J, Leither T, Kjellstrand C. Iatrogenic renal disease. Arch Intern Med 1991;151:1809-1812.
48. Chugh KS, Jha V, Sakhuja V, Joshi K. Acute renal cortical necrosis -- a study of 113 patients. Ren Fail 1994;16:37-47.
49. Galpin JE, Shinaberger JH, Stanley TM, et al. Acute interstitial nephritis due to methicillin. Am J Med 1978;65:756-765.
50. Shapiro SR, Bennett AH. Recovery of renal function after prolonged unilateral ureteral obstruction. J Urol 1976;115:136-140.
51. Bonventre JV. Mechanisms of ischemic acute renal failure. Kidney Int 1993;43:1160-1178.

52. Brezis M, Heyman SN, Dinour D, Epstein FH, Rosen S. Role of nitric oxide renal medullary oxygenation: studies in isolated and intact rat kidneys. J Clin Invest 1991;88:390-395.

53. Mason JC, Joeris B, Welsch J, Kriz W. Vascular congestion in ischemic renal failure: the role of cell swelling. Miner Electrolyte Metab 1989;15:114-124.

54. Kribben A, Wieder ED, Wetzels JFM, et al. Evidence for role of cytosolic free calcium in hypoxia-induced proximal tubule injury. J Clin Invest 1994;93:1922-1929.

55. Conger JD, Robinette JB, Hammond WS. Differences in vascular reactivity in models of ischemic acute renal failure. Kidney Int 1991;39:1087-1097.

56. Siegel NJ, Glazier WB, Chaudry IH, et al. Enhanced recovery from acute renal failure by the post ischemic infusion of adenine nucleotides and magnesium chloride in rats. Kidney Int 1980;17:338-349.

57. Rosen S, Spokes K, Brezis M, Silva P, Epstein FH. Toxicity of adenine nucleotides in the isolated perfused kidney: selective destruction of the S2 segment of the proximal tubule. Virchows Arch B Cell Pathol Incl Mol Pathol 1991;61:169-177.

58. Sevanian A, Kim E. Phospholipase A2 dependent release of fatty acids from peroxidized membranes. J Free Radic Biol Med 1985;1:263-271.

59. Schumer M, Colombel MC, Sawczuk IS, et al. Morphologic, biochemical, and molecular evidence of apoptosis during the reperfusion phase after brief periods of renal ischemia. Am J Pathol 1992;140:831-838.

60. Olsen S, Burdick JF, Keown PA, Wallace AC, Racusen LC, Solez K. Primary acute renal failure (`acute tubular necrosis') in the transplanted kidney: morphology and pathogenesis. Medicine (Baltimore) 1989;68:173-187.

61. Springer TA. Traffic signals for lymphocyte recirculation and leukocyte emigration: the multistep paradigm. Cell 1994;76:301-314.
62. Marks RM, Todd RF III, Ward PA. Rapid induction of neutrophil-endothelial adhesion by endothelial complement fixation. Nature 1989;339:314-317.
63. Weisman HF, Bartow T, Leppo MK, et al. Soluble human complement receptor type 1: in vivo inhibitor of complement suppressing post-ischemic myocardial inflammation and necrosis. Science 1990;249:146-151.
64. Grino JM. BN52021: a platelet activating factor antagonist for preventing post-transplant renal failure: a double-blind, randomized study. Ann Intern Med 1994;121:345-347.
65. Kelly KJ, Williams WW, Colvin RB, et al. Intercellular adhesion molecule-1 deficient mice are protected against ischemic renal injury. J Clin Invest 1996;97:1056-1063.
66. Granger DN, Korthuis RJ. Physiologic mechanisms of postischemic tissue injury. Annu Rev Physiol 1995;57:311-332.
67. Kelly KJ, Williams WW Jr, Colvin RB, Bonventre JV. Antibody to intercellular adhesion molecule 1 protects the kidney against ischemic injury. Proc Natl Acad Sci U S A 1994;91:812-816.
68. Haug CE, Colvin RB, Delmonico FL, et al. A phase I trial of immunosuppression with anti-ICAM-1 (CD54) mAb in renal allograft recipients. Transplantation 1993;55:766-772.

69. Troppmann C, Gillingham KJ, Benedetti E, et al. Delayed graft function, acute rejection, and outcome after cadaver renal transplantation. Transplantation 1995;59:962-968.

70. Halloran PF, Aprile MA, Farewell V, et al. Early function as the principal correlate of graft survival: a multivariate analysis of 200 cadaveric renal transplants treated with a protocol incorporating antilymphocyte globulin and cyclosporine. Transplantation 1988; 46:223-228.

71. Goes N, Urmson J, Ramassar V, Halloran PF. Ischemic acute tubular necrosis induces an extensive local cytokine response: evidence for induction of interferon-gamma, transforming growth factor-beta 1, granulocyte-macrophage colony-stimulating factor, interleukin-2, and interleukin-10. Transplantation 1995; 59:565-572.

72. Vakeva A, Meri S, Lehto T, Laurila P. Activation of the terminal complement cascade in renal infarction. Kidney Int 1995; 47:918-926.

73. Levin ER. Endothelins. N Engl J Med 1995;333:356-363 .

74. Hoste E, Physiological consequences of acute renal failure in the critically ill; Crit Care clin 2005; 21; 251-60.

75. Rose A; Hyperosmolar states; hyponatremia; Clinical physiology of acid base electrolyte disorders, fifth edition. NY.

76. Kellum A; Extracellular acidosis and the immune response. Clinical and physiological implications. Crit Care Clin 2004;8;331-6.

77. Bonventre JV, Zuk A, Ischemic ARF, an inflammatory disease? Kid Int 2004;66;480-485.

78. Vanholder R, De Smet R. pathophysiologic effects of uremic retention solutes. J Am soc Nephrol 1999;10;1815-23.

79. Bersentes TJ;Simmons DH. Effects of acute acidosis on renal hemodynamics. Am J Physiol ; 1967;212;633-40.

80. Finney SJ, Zekveld C, Elia A, Glucose control and mortality in critically ill patients ; JAMA; 2003;290;2041-7.

81. Subramanian S, Tomasz Z, Oliguria, volume overload, sodium balance and diuretics. Crit care clin 2005;21)291-303.

82. Pamela J. Fall, Hyponatremia and hypernatremia, A systematic approach to causes and their correction. Postgraduate medicine 2000 may 1, 107 (5).

83. Corrigan G, Ramaswamy D, Kwon O, Sommer FG, Alfrey EJ, Dafoe DC, Olshen RA, Scandling JD, Myers BD: PAH extraction and estimation of plasma flow in human postischemic acute renal failure. Am J Physiol 1999 ;277: F312–F318.

84. Perre C. Dagher , Stefan Herget-Rosenthal , Stefan G. Ruehm, Sang-Kyung Jo, Robert A. Star, , Rajiv Agarwal, and Bruce A. Molitoris; Newly Developed Techniques to Study and Diagnose Acute Renal Failure**,** J Am Soc Nephrol 2003;14:2188-2198.

85. Olbricht C, Mason J, Takabatake T, Hohlbrugger G, Thurau K: The early phase of experimental acute renal failure. II. tubular leakage and the reliability of glomerular markers. Pflugers Arch 1977; 372: 251–258.

86. Ramaswamy D, Corrigan G, Polhemus C, Boothroyd D, Scandling J, Sommer FG, Alfrey E, Higgins J, Deen WM, Olshen R, Myers BD: Maintenance and recovery

stages of postischemic acute renal failure in humans. Am J Physiol Renal Physiol 2002 ;282: F271–F280.

87. Bellomo, Defining , quantifying and classifying Acute renal failure ,Crit Care Clin;2005, 223-237.
88. Mucelli RP, Bertolotto M, Quaia E: Imaging techniques in acute renal failure. Contrib Nephrol 2001;132: 76–91.
89. Prasad PV, Edelman RR, Epstein FH: Noninvasive evaluation of intrarenal oxygenation with BOLD MRI. Circulation 1996 ;94: 3271–3275.
90. Harold Manning, Clay block, Prevention of acute renal failure in the critically ill. Am J resp med crit care 2002.; vol 165,320-324.
91. Bonventre JV, Weinberg JM. Kidney preservation ex vivo for transplantation

Annu Rev Med 1992;43:523-553.

92. Better OS, Stein JH. Early management of shock and prophylaxis of acute renal

failure in traumatic rhabdomyolysis. N Engl J Med 1990;322:825-829.

93. Shilliday I, Allison ME. Diuretics in acute renal failure. Ren Fail 1994;16:3-17.
94. Solomon R, Werner C, Mann D, D'Elia J, Silva P. Effects of saline, mannitol, and furosemide on acute decreases in renal function induced by radiocontrast agents. N Engl J Med 1994;331:1416-1420.
95. Weisberg LS, Kurnik PB, Kurnik BRC. Risk of radiocontrast nephropathy in patients with and without diabetes mellitus. Kidney Int 1994;45:259-265.

96. Weinstein JM, Heyman S, Brezis M. Potential deleterious effect of furosemide in radiocontrast nephropathy. Nephron 1992;62:413-415.

97. Lassnigg A, Donner E, Grubhofer G, Presterl E, Druml W, Hiesmayr M. Lack of renoprotective effects of dopamine and furosemide during cardiac surgery. J Am Soc Nephrol 2000; 11: 97-104.

98. Conger JD. Interventions in clinical acute renal failure: what are the data? Am J Kidney Dis 1995;26:565-576.

99. Sward K, Valson F, Ricksten SE. Long-term infusion of atrial natriuretic peptide (ANP) improves renal blood flow and glomerular filtration rate in clinical acute renal failure. Acta Anaesthesiol Scand 2001; 45: 536-542.

100. Allgren RL, Marbury TC, Rahman SN, Weisberg LS, Fenves AZ, Lafayette RA, Sweet RM, Genter FC, Kurnik BR, Conger JD, *et al* . . Anaritide in acute tubular necrosis. Auriculin Anaritide Acute Renal Failure Study Group. N Engl J Med 1997; 336: 828-834.

101. Lewis J, Salem MM, Chertow GM, Weisberg LS, McGrew F, Marbury TC, Allgren RL. Atrial natriuretic factor in oliguric acute renal failure. Anaritide Acute Renal Failure Study Group. Am J Kidney Dis 2000; 36: 767-774.

102. Redl-Wenzl EM, Armbruster C, Edelmann G, Fischl E, Kolacny M, Wechsler-Fordos A, Sporn P. The effects of norepinephrine on hemodynamics and renal function in severe septic shock states. Intensive Care Med 1993; 19: 151-154.

103. Klenzak J, Himmel farb J, Sepsis and the kidney , Crit Care Clin(2005) 211-222.

104. Luciano Gattinoni Luca Brazzi, M.D., Paolo Pelosi, M.D., Roberto Latini, M.D., Gianni Tognoni ; A Trial of Goal-Oriented Hemodynamic Therapy in Critically Ill Patients, NEJM October 19, 1995 Volume 333 (16):1025-1032.

105. Angstwurm MW, Schottdorf J, Schopohl J, Gaertner R. Selenium replacement in patients with severe systemic inflammatory response syndrome improves clinical outcome. Crit Care Med 1999; 27: 1807-1813.

106. Fishbane S, Durham JH, Marzo K, *et al.* N-acetylcysteine in the prevention of radiocontrast-induced nephropathy. J Am Soc Nephrol 2004;15;251–60.

107. Erica López Conesa *N*-acetyl-L-cysteine improves renal medullary hypoperfusion in acute renal failure Am J Physiol Regul Integr Comp Physiol 2001; 281: R730-R737.

108. Sort P, Navasa M, Arroyo V, Aldeguer X, Planas R, Ruiz-del-Arbol L, Castells L, Vargas V, Soriano G, Guevara M, *et al*. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. N Engl J Med 1999;341: 403-409.

109. Eisenman A, Armali Z, Enat R, Bankir L, Baruch Y. Low-dose vasopressin restores diuresis both in patients with hepatorenal syndrome and in anuric patients with end-stage heart failure. J Intern Med 1999; 246: 183-190 .

110. Uriz J, Gines P, Cardenas A, Sort P, Jimenez W, Salmeron JM, Bataller R, Mas A, Navasa M, Arroyo V, *et al* . Terlipressin plus albumin infusion: an effective and safe therapy of hepatorenal syndrome. J Hepatol 2000; 33: 43-48 .

111. Kleinknecht, D.. Uremic and non-uremic complications in acute renal failure: evaluation of early and frequent dialysis on prognosis. Kidney Int 1972.. 1: 190-196.

112. Davenport, A., E. J. Will, and A. M. Davidson.. Improved cardiovascular stability during continuous modes of renal replacement therapy in critically ill patients with acute hepatic and renal failure. Crit. Care Med1993. 21: 328-338.

113. Karsou, S. A., B. L. Jaber, and B. J. G. Pereira. Impact of intermittent hemodialysis variables on clinical outcomes in acute renal failure. Am. J. Kidney *Dis.* 2000. 35: 980-991.

114. Schiffl, H., S. M. Lang, A. Konig, and E. Hald. Dose of intermittent hemodialysis (IHD) and outcome of acute renal failure (ARF): a prospective randomized study J. Am. Soc1997.. Nephrol. 8: 290A .

115. Michael J, Metnitz P, epidemiology and natural history of ARF in the ICU. Crit Care Clin2005 239-249.

116. McCarthy JT: Prognosis of patients with acute renal failure in the intensive-care unit: A tale of two eras. Mayo Clin Proc 1996.71 : 117 –126.

117. Feest TG, Round A, Hamad S: Incidence of severe acute renal failure in adults: Results of a community based study. BMJ 1993.306 : 481 –483.

118. Morgera et al. in the long term outcome of patients recovered from acute renal failure who had received continuous renal replacement therapy .Am journal of kidney diseases. 2002 ;40 (2) 275-9.

119. Maynard et al . quality of life and dialysis decisions in critically ill patients with acute renal failure . Intensive care medicine 2003, 29(9);1589-93.

120. Rinaldo Bellomo, Claudio Ronco , John A Kellum , Ravindra L Mehta , Paul Palevsky and the ADQI workgroup. Acute renal failure – definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI)Group. Critical Care clin 2004, 8:R204-R212 .

121. Kroupa J , Definition of "polytrauma" and "polytraumatism" Acta Chir Orthop Traumatol Cec.1990 Jul;57(4):347-60.

122. Nihal Y Abosaif, Yasser T, Heap M, Russel J. The outcome of ARF in the intensive care unit according to RIFLE; model application, sensitivity, and predictability. Am J Kid Dis 2005;46;6;1038-1-48.

123. Uchino, KellumJ, Bellomo R, Doig G, Acute renal failure in critically ill patients, a multinational multicenter study. JAMA 2005.294;7;813-818.

124. Flavio L, Daliana P, Serial evaluation of the SOFA score to predict outcome in critically ill patients. JAMA, 2001, 286,14,1754-1757.

125. Rangel frausto, MS, Pittet D, Costigan M et al. the natural history of systemic inflammatory response system. A prospective study. JAMA 1995;273(2),117-23.

126. Brun Buisson C,meshaka P, Pinton P, et al. Episepsis a reappraisal of the epidemiology an d outome of severe sepsis in French intensive care units. Intensive care medicine 2004;30(4);580-588.

127. Klenzak J, Himmel farb J, Sepsis and the kidney , Crit Care Clin(2005) 211-222.

128. Michael J, Metnitz P, epidemiology and natural history of ARF in the ICU. Crit Care Clin(2005) 239-249.

129. Arabi Y, Ahmed, Haddad. S . et al. Outcome predictors of cirrhosis patients admitted to the surgical intensive care unit. European journal of gastroenterology and hepatology 2004; 16(3);333-39.

130. Mattana J, Singhal PC. Prevelance and determinants of acute renal failure following cardiopulmonary resuscitation. Arch.Int.med. 1993;153(2);235-9.

131. Ravindra L. Mehta, MD; Maria T. Pascual, RN, MPH; Sharon Soroko, MS; Glenn M.Chertow, MD, MPH; for the PICARD Study Group Diuretics, Mortality, and Nonrecovery of Renal Function in Acute Renal Failure JAMA. 2002;288:2547-2553.

132. Norbert Lameire, Raymond Vanholder, and Wim Van Biesen Loop Diuretics for Patients With Acute Renal Failure: Helpful or Harmful? JAMA.2002;288:2599-2601.

133. Sushrut , GaryC. Curhan,Ron Wald, Ellen McCarthy and Glenn Chertow Declining mortality in patients with acute renal failure 1988 to 2002, American journal of nephrology January 2006.

134. Mangano DT, Preoperative assessment of the patient with cardiac disease. CurrOpiCardiol.1995 Sep;10(5):530-42.Review.

Appendix 1

Simplified MDRD (Modification of diet in renal disease)[120] formula for estimation of baseline creatinine

Age (years)	Black males (mg/dl [μmol/l])	Other males (mg/dl [μmol/l])	Black females (mg/dl [μmol/l])	Other females (mg/dl [μmol/l])
20–24	1.5 (133)	1.3 (115)	1.2 (106)	1.0 (88)
25–29	1.5 (133)	1.2 (106)	1.1 (97)	1.0 (88)
30–39	1.4 (124)	1.2 (106)	1.1 (97)	0.9 (80)
40–54	1.3 (115)	1.1 (97)	1.0 (88)	0.9 (80)
55–65	1.3 (115)	1.1 (97)	1.0 (88)	0.8 (71)
>65	1.2 (106)	1.0 (88)	0.9 (80)	0.8 (71)

Appendix 2 : SOFA(Sequential Organ Failure Assessment) Score[124]

SOFA score	0	1	2	3	4
Respiration PaO_2/FIO_2 (mm of hg)	>400	301-400	201-300	101-200	<=100
Coagulation Platelets (x 10^3)	>150	101-150	51-100	21-50	<20
Liver Bilirubin(mg%)	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	>12.0
Cardiovascular Hypotension	No hypotension	MAP<70 mm hg	Dopamine<5 mcg/kg/min or Dobutamine (any dose)	Dopamine >5 mcg/kg/min	Dopamine >15 mcg/kg/min
CNS (GCS)	15	13-14	10-12	6-9	<6
Renal Creatinine (mg%) Urine output	<1.2	1.2-1.9	2.0-3.4	3.5-4.9 <500 ml/day	>5.0 <200 ml/day

Appendix 3
ARF STUDY PROFORMA

Serial no

Name : sex M/F Age :
Date of admission into ICU Date of Discharge from ICU
Diagnosis

Inclusion criteria RISK Rise in serum creatinine by 1.5 times
Urine output<0.5 ml/kg/hr for 6 hours
OR
INJURY Rise in serum creatinine by 2 times
Urine output<0.5 ml/kg/hr for12 hours
OR
FAILURE Rise in serum creatinine by 3 times
Serum creatinine >4 mg% and acute rise in serum creatinine by more than 0.5%
Urine output<0.3 ml/kg/hr for 6 hours

Pre morbid creatinine: if known:

Number of Ventilator days: Infection at admission: yes/no

Organ system failure:

CVS	yes/no	RS	yes/no	Hematological	yes/no	CNS	yes/no	Liver	yes/no

APACHE II (worst score in the first 24 hours) **(A)**											
Temp	MAP	HR	RR	AaO_2/PaO_2	GCS	pH	PCV	TC	Na	K	Creat
Age Score (**B)**					APACHE Predicted Mortality rate %						
Chronic health point score **(C)**					APACHE Adjusted Mortality rate %						
Total score APACHE = **A+B+C=**											
SOFA (worst score in the first 24 hours) Total SOFA =											
Respiration	Coagulation	CVS	Hematological	CNS	Hepatic						

Physiological	Day 1	Day2	Day3	Day4	Day5	Day6	Day7
Heart rate							
Resp rate							
MAP							
CVP							
Temp							
Urine output							
GCS							
Lab values							
Blood sugar							
Lactate							
PaO_2							
FiO_2							
$PaCO_2$							
pH							
Platelet							
Creatinine							
Bilirubin							
Na							
K							
Total WBC							
PCV							
Intervention							
Diuretics							
N Acetyl Cysteine							
Ionotropes							
Mechanical ventilation							
RRT							

Number of surgeries:

Emergency/ Elective surgeries:

Pre existing chronic diseases :

Outcome : Survivor / Non survivor

Appendix 4

APACHE II SCORING . TOTAL SCORE = A+B+C

Table A

Physiological variable	+4	+3	+2	+1	0	+1	+2	+3	+4
Temperature (□)	> 41	39-40.9		38.5-38.9	36-38.4	34-35.9	32-33.9	30-31.9	< 29.9
Mean arterial pressure (mmHg)	> 160	130-159	110-129		70-109		50-69		< 49
Heart rate (ventricular response)	> 180	140-179	110-139		70-109		55-69	40-54	< 39
Respiratory rate (non-vetilated or ventilated)	> 50	35-49		25-34	12-24	10-11	6-9		< 5
Oxygenation: **$AaDO_2$ or PaO_2** (mmHg)(FiO_2 > 0.5 record $AaDO_2$, FiO_2 <0.5 record PaO_2)	> 500	350-499	200-349		<200 PaO_2 >70	PaO_2 61-70		PaO_2 55-60	PaO_2 <55
Arterial pH	> 7.7	7.6-7.69		7.5-7.59	7.33-7.49		7.25-7.32	7.15-7.24	<7.15
Serum sodium (mmol/l)	> 180	160-179	155-159	150-154	130-149		120-129	111-119	< 110
Serum potassium (mmol/l)	> 7	6-6.9		5.5-5.9	3.5-5.4	3-3.4	2.5-2.9		< 2.5
Serum creatinine (mg/dl) (double point score for acute renal failure)	> 3.5	2-3.4	1.5-1.9		0.6-1.4		<0.6		
Hematocrit (%)	> 60		50-59.9	46-49.9	30-45.9		20-29.9		<20
W.B.C. (´ $10^2/mm^3$)	> 40		20-39.9	15-19.9	3-14.9		1-2.9		<1
Glasgow coma score (GCS) Score =15- actual GCS									
Serum HCO_3 (venous-mmol/l) (not preferred, use if no ABGs)	> 52	41-51.9		32-40.9	22-31.9		18-21.9	15-17.9	<15

Table B: Age Points

Age	< 44	45 ~ 54	55 ~ 64	65 ~ 74	> 75
Score	0	2	3	5	6

Ref : critical care medicine 1985;13;818-829.

TABLE C: Chronic Health Points (CHP)

1. Assigned if the patient has a history of severe organ system insufficiency or is immunocompromised.

2. For non-operative or emergency post-operative patients, 5 points; and for elective post-operative patients, 2 points.

3. Organ insufficiency or an immunocompromised state must have been evident before hospital admission and must conform to the following criteria: ***Liver***: biopsy proven cirrhosis and documented portal hypertension, episodes of past upper gastrointestinal bleeding attributed to portal hypertension, or prior episodes of hepatic failure/encephalopathy/coma. ***Cardiovascular***: New York Heart Association Class IV (i.e. symptoms of angina or cardiac insufficiency at rest or during minimal exertion).***Respiratory***: chronic restrictive, obstructive, or vascular disease resulting in severe exercise restriction, i.e. Unable to climb stairs or perform household duties, or documented chronic hypoxia, hypercapnia, secondary polycythemia, severe pulmonary hypertension (>40 mmHg), or respirator dependency.***Renal***: receiving chronic dialysis. ***Immunocompromised***: the patient has received therapy that suppress resistance to infection, e.g. immunosuppression, chemotherapy, radiation, long term or recent high dose steroids, or has a disease that is sufficiently advanced to suppress resistance to infection, e.g. Leukemia lymphoma, AIDS.

APPENDIX 5

APACHE II expected mortality

0-4 = 4% death rate	10-14 = 15% death rate	20-24 = 40% death rate	30-34 = 75% death rate
5-9 = 8% death rate	15-19= 25% death rate	25-29 = 55%death rate	>34 = 85% death rate

APPENDIX 6 APACHE ADJUSTED DEATH RATE

Adjusted death rate	Logit = -3,517+(Apache II) * 0,146 + Diagnostic category weight Predicted Death Rate =$e^{Logit}/(1+e^{Logit})$
0	Diagnostic category weight (y)= 0 (a point for decimals)

Nonoperative	y	Postoperative patients	y	y (if emergency)
Respiratory failure or insufficiency from:		Multiple trauma	-1.684	-1.081
Asthma / allergy	-2.108	Admission due to chronic cardiovascular disease	-1.376	-0.773
COPD	-0.367	Peripheral vascular surgery	-1.315	-0.712
Pulmonary edema (noncardiogenic)	-0.251	Heart valve surgery	-1.261	-0.658
Postrespiratory arrest	-0.168	Craniotomy for neoplasm	-1.245	-0.642
Aspiration / poisoning / Toxic	-0.142	Renal surgery for neoplasm	-1.204	-0.601
Pulmonary embolus	-0.128	Renal Transplant	-1.042	-0.439
Infection	0	Head trauma	-0.955	-0.352
Neoplasm	0.891	Thoracic surgery for neoplasm	-0.802	-0.199
Cardiovascular failure or insufficiency from :		Craniotomy for ICH/ SDH/ SAH	-0.788	-0.185
Hypertension	-1.798	Laminectomy and other spinal cord surgery	-0.699	-0.096
Rythm disturbance	-1.368	Hemorrhagic shock	-0.682	-0.079
Congestive heart failure.	-0.424	GI Bleeding	-0.617	-0.014
Hemorrhagic shock / hypovolemia	0.493	GI surgery for neoplasm	-0.248	0.355
Coronary artery disease	-0.191	Respiratory insufficiency	-0.140	0.463

Sepsis	0.113	GI perforation / obstruction	0.060	0.663
Post cardiac arrest	0.393	If not in one of the above, which major vital organ system led to ICU admission post surgery		
Cardiogenic shock	-0.259	Neurologic	-1.150	-0.574
Dissecting thoracic / abdominal aneurysm	0.731	Cardiovascular	-0.797	-0.194
Trauma		Respiratory	-0.610	-0.007
Multiple trauma	- 1.228	Gastro-intestinal	-0.613	-0.01
Head injury	-0.517	Metabolic / renal	-0.196	0.407
Neurologic				
Seizure disorder	-0.584			
ICH/ SDH/ SAH	0.723			
Other				
Drug overdose	-3.353			
Diabetic ketoacidosis	-1.507			
GI Bleeding	0.334			
If not in one of the groups above, which major organ system was the principal reason for admission:				
Metabolic / renal	-0.885			
Respiratory	-0.890			
Neurologic	-0.759			
Cardiovascular	0.470			
Gastrointestinal	0.501			

APPENDIX 7

Sepsis [23] was defined as evidence of serious bacterial infection in which two or more of the following were present. Proven or suspected microbial etiology with features of SIRS such as

- Core body temperature >38 or <36 ^{0} C,
- Heart rate more than 90/Min,
- Respiratory rate more than 20, or PaCO2 <32 mm of hg or need for mechanical ventilation,
- White blood cell count >12 000 cells per mm^3 or < 4000 /mm^3 with more than 10%band forms

Polytrauma was defined as either an unstable pelvic fracture requiring more than 6 units of whole blood or packed red cells, or presence of two or more long bone fractures , or presence of a pelvic fracture with long bone fracture and a hollow viscus injury [121] .

Cardiovascular dysfunction was defined as a need for vasoactive medication, despite adequate filling up of the intravascular volume based on the central venous pressures.

Pulmonary dysfunction was defined as need for mechanical ventilation.

Hematological failure when the Platelet count were less than 100,000/mm^3 .

Liver dysfunction was defined with bilirubin levels greater than 2mg%. Patients with pre existing chronic liver disease were screened for a rise in bilurubin levels before defining them.**Use of diuretics** was defined as administration of either bolus doses or continuous infusion of diuretics.

Systemic Infection at admission was defined as

- fever (> 38 °C) with or without chills.

- hypotension (systolic pressure <= 90 mm Hg)
- With or without positive blood cultures
- Appropriate antibiotic therapy being initiated on admission by the clinician

APPENDIX 8

Coding for master sheet

A Hospital number
B Age
C - Sex 0-male,1- female
D- Number of hospital days
E Number of ICU days
F- Inclusion criteria - 1 - risk, 2 - injury, 3- failure
G Mortality 1-yes, 0- no
H – APACHE
I – APACHE predicted mortality
J - APACHE adjusted mortality
L – DIAGNOSIS Sepsis - 1, Trauma- 2, crush syndrome-3, hepato renal syndrome-4,acute cardiogenic failure - 5, major surgery- 6, obstructive renal faliure- 7, renal parenchymal causes- 8 ,acute respiratory failure- 9, pancreatitis 10, -hemorrhagic shock 11
M- Organ failure 0-nil,1- one organ failure,2 two organ failure, 3- three organ failure, 4 four organ failure, 5 five organ failure
N- CVS failure 1- yes, 0 – no
O- Respiratory failure 1 - yes , 0- no
P - Hematological failure 1 -yes, 0- no
Q - Hepatic failure 1 -yes, 0- no
R – CNS failure 1 - yes, 0- no
S – Pre morbid creat 1- normal, 2 abnormal, 3 not known
T Bilirubin
U- Infection at admission 1- Yes, 0- no
V – Major surgery 1-yes, 0 - no
W systems involvement before arf 0 - nil,1- one system, 2- two system, 3- three system,4- four system, 5- five system
X systems involvement after arf 0 - nil,1- one system, 2- two system, 3- three system,4- four system, 5- five system
Y – Duration of ICU stay in days before inclusion into study
Z- pre existing chronic illness 1yes, 0- no
AA- Type of chronic disease 0- nil,1- diabetes mellitus,2- malignancy,3- ischemic heart/rhythm disorders, 4- urological disease, 5 chronic liver disease,6 - hypertension, 7-chronic respiratory failure ,8 pancreatitis 9- malignancy,10- combination of 2 system disorders,11- combinanation of three system disorders
AB- use of diuretics
AC - use of acetyl cysteine - 1- yes, 0- no
AD - use of ionotropes 1- yes, 0- no
AE mechanical ventilation 1- yes, 0- no
AF mean arterial pressure at admission
AG CVP at admission

AH SOFA at admission
AI pH at admission
AJ – lactate at admission
AK – admission creatinine
AL – blood sugar at admission
AM admission urine
AN renal replacement therapy 1 –yes, 0 no
AO indication for renal replacement- 0 nil, 1-hyperalemia,2- severemetabolic acidosis, 3 fluid overload, 4 rising creatinine, 5 oliguria
AP Nno of sittings of dialysis
AQ – Number of surgeries
AR - Ttype of surgery- 0 -no surgery , 1- emergency, 2 -elective

hospital nu	age	se	hos	icu	inc	mc	apa	apa	ap	ven	dia	or	cv	res	he	he	cn	pre	bilirı	infe	ma	sy	sy	icu	pre	typ	us	us	use
832742C	29	0	20	9	2	0	14	19	16	8	1	5	1	1	1	1	0	3	19	1	0	3	1	0	0	0	1	0	1
831367c	75	0	22	12	2	0	20	36	31	12	1	4	0	1	1	1	0	3	6.7	1	0	3	0	0	0	0	1	0	1
831565c	60	0	14	3	1	0	18	29	18	0	8	2	0	1	0	0	0	3	1.7	0	1	1	0	0	1	8	0	0	0
804174c	40	0	25	11	1	0	11	12	13	9	1	4	1	1	0	1	0	3	2.4	1	1	2	1	0	0	0	1	0	1
804052c	27	0	13	8	1	0	20	35	16	8	2	3	1	1	0	0	0	3	1	0	1	2	0	0	0	0	0	0	1
802285c	33	0	19	1	1	0	22	42	54	0	9	1	0	0	0	0	0	1	0.5	1	1	0	0	0	1	8	0	0	0
789426c	45	0	7	2	1	0	15	21	7	0	2	1	0	0	0	0	0	1	1	0	0	0	0	0	1	6	0	0	0
937227B	52	0	71	4	1	0	19	32	41	2	1	4	1	1	1	0	0	1	0.4	1	0	2	0	0	1	9	0	0	1
227995C	21	1	31	8	3	0	21	42	58	7	1	4	1	1	1	0	0	1	0.8	1	1	2	2	0	0	0	1	0	1
815843C	28	0	28	4	2	0	17	26	40	0	1	2	1	0	0	0	0	1	0.4	1	0	1	0	0	0	0	0	0	1
807315C	25	1	22	11	1	0	23	46	43	8	11	5	1	1	1	0	0	1	0.7	1	1	3	0	0	0	0	0	0	1
789111C	22	1	7	1	1	0	19	32	30	1	11	3	1	0	1	0	0	1	2.9	0	1	1	1	0	0	0	0	0	0
767280C	47	0	19	1	1	0	12	12	4	1	6	1	0	0	0	0	0	1	0.9	0	1	0	0	0	1	3	1	0	0
780728c	15	1	12	3	1	0	14	18	26	1	9	2	0	1	0	0	0	1	0.6	1	1	1	0	0	1	4	0	1	0
717285c	28	0	36	1	1	0	16	23	11	1	6	1	0	0	0	0	0	1	0.6	0	1	0	0	0	1	5	0	0	0
214768A	76	0	5	2	1	0	28	63	63	0	1	2	1	0	0	0	0	1	1	0	0	1	0	0	1	4	1	0	1
824533C	51	0	7	2	1	0	10	11	4	1	2	1	0	0	0	0	0	3	1	0	1	0	0	0	1	6	0	0	0
812288C	60	0	25	1	2	0	18	29	9	0	6	1	0	0	0	0	0	2	1	0	1	0	0	0	1	11	0	0	0
818657C	66	0	11	6	2	0	22	42	58	6	9	2	0	1	0	0	0	3	0.8	0	1	1	0	0	1	10	1	0	0
810383c	69	0	24	7	1	0	20	36	14	6	6	3	1	1	0	0	0	1	0.5	0	1	0	2	0	1	4	1	0	1
824752C	44	1	28	2	2	0	17	26	22	2	5	2	1	0	0	0	0	1	1	0	1	1	0	0	1	3	0	0	0
802327C	65	1	12	6	1	0	16	23	37	5	3	2	0	1	0	0	0	1	1	0	1	0	1	0	1	10	1	0	0
839468C	47	0	10	1	1	0	10	11	3	1	6	1	0	0	0	0	0	1	1	0	1	0	0	0	1	6	0	0	0
839487C	65	0	7	2	1	0	15	21	10	0	2	2	0	1	0	0	0	3	0.9	0	0	1	0	0	1	10	0	0	0
846244C	58	0	8	3	1	0	13	17	28	3	1	2	1	0	0	0	0	1	1	1	1	1	0	0	0	0	1	1	1
832528C	85	0	17	1	3	0	18	46	62	0	7	1	0	0	0	0	0	1	1	0	1	0	0	0	1	6	0	0	0
775245C	60	1	15	2	1	0	9	10	18	2	6	1	0	0	0	0	0	1	0.6	0	1	0	0	0	1	6	0	1	1
552686c	45	1	9	3	3	0	21	39	55	3	1	4	1	1	1	0	0	3	0.8	1	1	2	0	0	0	0	1	1	1
830061C	45	0	7	2	2	0	14	19	31	2	1	2	1	0	0	0	0	3	0.6	1	1	1	0	0	0	0	0	1	1
860605C	26	0	40	9	2	0	10	11	8	9	2	3	1	0	0	0	1	1	0.7	0	1	2	0	0	0	0	1	0	1
856330C	37	1	5	2	1	0	14	19	31	1	11	2	1	0	0	0	0	3	0.6	0	1	1	0	0	0	0	0	0	1
827396C	43	1	30	7	2	0	15	21	28	7	1	3	1	1	0	0	0	1	2.3	1	1	2	0	0	1	6	1	1	1
360605C	48	0	10	5	2	0	12	15	21	3	1	3	1	1	0	0	0	3	0.8	1	1	2	0	0	1	1	1	0	0
801557C	23	1	70	1	2	0	9	10	11	1	4	5	1	1	1	1	1	3	1.1	1	0	3	1	0	0	0	0	0	0
789770C	34	0	10	4	1	0	10	11	10	2	2	1	0	0	0	0	0	3	0.8	1	0	1	0	0	1	9	1	1	1
298849C	23	1	8	1	1	0	11	13	13	0	4	2	0	0	1	0	0	1	13	0	0	1	0	0	0	0	0	0	0
789197c	32	0	14	3	1	0	5	6	11	3	1	2	1	1	0	0	0	3	1.8	1	1	1	1	0	0	0	0	0	1
699898a	45	0	21	2	2	0	16	24	38	2	1	3	1	1	0	0	0	3	0.8	1	1	0	0	0	1	6	0	1	1
789949c	44	0	33	6	1	0	18	29	12	5	2	2	1	0	1	0	0	1	0.9	0	1	2	0	0	0	0	1	0	1
756819c	44	0	41	2	1	0	12	14	12	2	1	3	1	0	1	0	0	1	1.1	1	1	2	0	0	1	10	0	1	1
780072b	60	0	20	8	3	0	23	46	58	7	1	3	1	1	0	0	0	3	0.7	1	1	2	0	0	1	10	1	1	1
834535c	47	1	12	5	1	0	15	21	21	4	1	3	1	1	0	0	0	1	1.1	1	1	2	1	0	0	0	0	1	1
832924c	52	1	20	1	3	0	21	38	41	0	4	3	1	0	0	1	0	1	27	1	0	1	1	0	1	6	0	0	0
196173C	27	0	20	6	1	0	17	26	23	6	1	3	1	1	0	0	0	3	0.9	1	1	2	0	0	0	0	0	1	1
846162C	31	0	43	2	1	0	4	5	3	2	2	2	1	0	0	0	0	1	0.8	0	1	1	0	0	0	0	0	0	1
839476C	23	0	11	2	1	0	11	13	19	1	9	2	0	1	0	0	0	1	0.9	0	1	1	0	0	0	0	0	0	0
845811C	55	0	19	6	3	0	19	32	48	5	1	3	1	1	0	0	0	1	1	1	1	1	1	0	1	1	1	1	1
839188C	50	0	7	5	2	0	12	14	6	4	2	3	1	1	0	0	0	1	0.6	0	1	2	0	0	1	6	0	1	0
828232C	35	0	9	4	1	0	11	13	19	4	1	2	0	1	0	0	0	1	0.4	0	1	2	0	0	0	0	0	0	1
571893C	34	0	40	10	3	0	24	49	59	10	4	5	1	1	1	1	0	1	7	0	1	3	1	0	0	0	1	1	1

820021C	46	1	28	11	1	0	13	17	28	10	1	3	1	1	0	0	0	1	1.9	1	1	1	1	0	1	1	0	0	1
818563C	34	0	3	2	1	1	19	32	32	2	2	3	1	1	0	0	0	3	1	0	1	2	0	0	0	0	1	0	1
767691A	75	1	3	3	2	1	32	76	82	3	1	3	1	1	0	0	0	1	0.9	1	1	2	0	0	1	10	1	0	1
823419C	62	1	38	24	2	1	19	32	41	22	1	4	1	1	1	0	0	1	1.8	1	1	2	1	13	1	8	1	0	1
851199C	39	0	2	1	3	1	23	46	62	1	1	5	1	1	1	1	1	3	3.5	1	1	3	2	0	0	0	1	0	1
790386C	37	0	6	4	2	1	32	76	78	3	1	3	1	1	0	1	0	2	1.5	1	1	2	0	0	1	5	1	0	1
804486C	47	0	4	4	3	1	33	78	87	4	1	4	1	1	1	0	0	3	1.1	1	1	2	1	0	0	0	0	1	1
831974C	36	0	5	3	3	1	25	53	63	5	1	3	1	1	0	0	0	1	1	1	1	2	1	0	0	0	1	1	1
804248C	37	0	20	11	2	1	21	39	49	9	3	3	1	0	1	0	0	1	1.3	0	1	1	1	0	1	1	1	1	1
433307B	67	0	7	4	3	1	27	61	75	4	1	3	1	0	1	0	0	3	0.9	1	1	1	1	0	0	0	1	0	1
789407C	56	0	1	1	3	1	34	81	89	1	1	4	1	1	1	0	0	1	1.6	1	1	2	1	0	0	0	1	1	1
837723C	48	0	46	2	1	1	13	17	17	1	5	2	1	0	0	0	0	1	1	0	0	1	0	0	1	3	0	0	1
777323C	39	0	4	1	1	1	31	73	80	1	5	2	1	0	0	0	0	3	0.6	0	0	1	0	0	0	0	0	0	1
784850C	53	0	16	9	2	1	15	21	18	9	1	4	1	1	0	1	0	1	1.8	0	1	2	1	5	1	6	1	1	1
814614C	36	1	7	4	1	1	20	36	37	5	1	3	1	1	0	0	0	1	0.6	0	1	2	0	5	1	5	1	1	1
789083C	37	0	2	2	3	1	23	46	62	3	11	2	1	0	0	0	0	3	1	0	1	1	0	0	0	0	1	0	1
753790C	65	1	15	6	2	1	19	49	48	6	1	4	1	1	1	0	0	3	0.9	1	0	2	1	0	1	1	1	1	1
087763B	65	0	4	4	1	1	25	53	69	4	1	4	1	1	1	0	0	3	0.7	1	1	2	1	0	1	1	1	1	1
839241C	52	0	3	3	1	1	18	29	44	3	1	4	1	1	1	1	0	3	3	1	1	2	2	0	1	1	0	0	1
814833C	56	0	13	11	2	1	29	67	75	10	1	4	1	1	1	0	0	1	0.6	0	1	2	1	10	1	6	1	1	1
840506C	39	0	2	2	1	1	19	32	48	2	1	4	1	1	1	1	0	3	2.2	1	1	2	1	0	0	0	0	0	1
818562C	37	0	9	8	3	1	23	48	62	8	1	5	1	1	1	1	0	3	3.6	1	1	3	1	0	0	0	1	1	1
822215C	55	0	12	7	2	1	25	54	63	7	4	4	1	1	0	1	0	1	11	1	1	2	1	0	1	1	1	1	1
789175C	34	0	2	2	2	1	28	64	74	2	1	4	1	1	1	1	0	3	2.6	1	1	2	2	0	1	8	1	0	1
714553C	71	1	2	2	1	1	28	64	78	2	5	4	1	1	1	0	0	3	0.9	1	1	2	1	0	1	3	1	0	1
368098C	63	0	7	2	2	1	31	73	84	2	1	4	1	1	1	0	0	3	0.5	1	1	2	1	0	1	2	0	0	1
789200C	39	1	10	2	3	1	23	56	72	6	1	4	1	1	1	1	0	1	2.1	1	1	3	1	0	0	0	1	1	1
700835A	82	0	1	1	2	1	30	70	78	1	5	3	1	1	0	0	0	1	0.5	0	0	1	0	0	1	7	0	0	1
571893C	55	0	48	1	2	1	23	46	59	1	4	2	0	0	0	1	0	1	19	0	0	1	0	0	1	5	1	0	1
169695C	48	1	6	2	3	1	27	61	71	1	5	3	1	1	0	0	0	1	2.7	1	1	1	1	0	1	5	1	0	1
714553B	71	1	2	2	1	1	23	46	62	2	1	2	1	0	0	0	0	3	0.8	1	1	1	0	0	1	10	1	0	1
832557C	52	0	23	15	3	1	28	64	73	15	3	4	1	1	1	0	0	1	0.4	0	1	0	3	0	1	1	1	1	1
4470	74	0	10	10	3	1	28	64	78	10	1	4	1	1	1	0	0	1	0.7	1	1	2	1	0	1	10	1	1	1
818518C	69	0	21	4	2	1	34	81	89	3	1	5	1	1	1	1	0	1	6.6	1	1	2	2	0	1	10	1	1	1
823581C	40	0	9	2	3	1	25	50	66	5	1	4	1	1	1	0	0	1	2	1	1	2	1	0	0	0	1	0	1
828264C	38	0	3	3	3	1	28	63	78	3	1	3	1	1	1	0	0	3	5	1	1	2	1	0	0	0	0	0	1
832988C	19	0	1	1	3	1	23	46	56	1	1	4	1	1	1	0	0	3	1.5	1	1	2	2	0	0	0	1	0	1
833062C	58	1	11	5	2	1	28	64	74	5	1	4	1	1	1	0	0	1	1.7	1	1	2	2	0	1	1	1	1	1
800100C	55	0	9	6	3	1	25	53	63	3	3	2	1	0	0	0	0	3	0.9	1	1	1	0	0	1	1	1	0	1
817095C	63	0	11	9	2	1	20	35	45	9	1	3	1	1	0	0	0	1	1.9	1	1	1	1	7	1	10	1	1	1
480352B	66	1	7	7	1	1	25	53	56	7	1	3	1	1	0	0	0	1	1	1	1	1	1	0	1	1	1	0	1
789332C	61	0	8	8	2	1	24	50	61	8	1	3	1	1	0	0	0	3	0.9	1	1	1	1	0	1	10	1	0	1
846193C	51	0	19	19	1	1	17	26	41	19	1	4	1	1	1	0	0	1	1.5	1	1	2	1	9	1	1	1	1	1
426783B	61	0	18	8	1	1	28	63	73	8	1	4	1	1	1	0	0	1	1.2	1	1	2	1	0	1	6	1	0	1
774355C	67	0	39	13	1	1	25	53	62	13	1	4	1	1	1	0	0	1	0.8	1	1	2	1	0	1	2	1	0	1
454868C	66	1	1	1	2	1	27	60	74	1	1	3	1	1	1	0	0	1	1.3	1	1	2	1	0	1	1	1	0	1
804213C	29	0	15	15	1	1	11	13	22	15	1	4	1	1	0	1	0	1	4.1	1	1	3	1	0	0	0	1	1	1

me	mear	CVP	sofa	admiss	lactat	adm	adm.	Adm	ren	indi	no c	nun	type of surgery
1	53	2	11	7.26	3	1.9	216	2.8	0	0	0	1	0
1	90	13	11	7.41	14	3.8	132	2.3	0	0	0	3	1
0	93	12	7	7.34	0.6	2.1	94	2.5	0	0	0	1	2
1	53	12	12	7.16	2.4	1.4	141	1.7	0	0	0	1	1
1	40	2	8	6.98	9	1.6	136	2.3	0	0	0	2	1
0	83	0	4	7.25	2	2.2	159	1.9	0	0	0	1	1
0	110	8	4	7.32	1.9	1.9	129	1.6	0	0	0	0	0
1	53	3	5	7.23	1.7	1.7	493	1	0	0	0	1	2
1	53	6	10	7.45	7	3.6	130	0.6	1	5	9	1	2
0	67	7	7	7.36	3	1.7	114	1.4	0	0	0	2	2
1	57	6	10	7.26	2.4	1.5	164	2.6	0	0	0	2	1
1	63	10	9	7.27	2.1	1.8	130	1.4	0	0	0	0	1
1	77	12	2	7.37	1.4	1.5	129	1.4	0	0	0	0	1
1	57	0	3	7.05	5	1.4	229	1.5	0	0	0	1	2
1	57	2	1	7.2	6.3	1.6	129	1.7	0	0	0	1	2
0	70	3	6	7.28	1.9	1.6	191	1.6	0	0	0	1	2
0	83	6	3	7.31	1.9	1.5	150	0.8	0	0	0	1	1
0	83	6	5	7.36	1.1	4	105	1	0	0	0	1	2
1	83	13	6	7.25	1.4	3.4	156	1.6	0	0	0	1	1
1	43	4	2	7.24	1.6	1.8	131	1.1	0	0	0	1	2
1	60	26	4	7.5	1.3	2.7	104	1.1	0	0	0	2	2
1	80	15	1	7.32	1.6	1.8	107	1.3	0	0	0	1	1
1	90	14	1	7.36	1.1	1.8	124	2.1	0	0	0	1	2
0	120	10	4	7.41	1	2	145	1.4	0	0	0	0	0
0	70	8	7	7.38	1.9	1.6	134	1.2	0	0	0	1	1
0	87	8	5	7.32	1.6	3.1	126	0.8	0	0	0	1	1
1	73	2	7	7.45	1	1.4	313	0.9	0	0	0	1	2
1	78	21	11	7.31	2.1	8.6	131	0.6	1	4	3	1	1
1	86	8	6	7.32	2.2	2.2	113	1	0	0	0	1	1
1	83	10	10	7.49	1.1	1.3	104	1.3	0	0	0	2	1
1	63	2	11	7.28	2.2	1.5	108	1.6	0	0	0	1	1
1	53	3	8	7.23	4.2	2.3	161	0.6	1	4	6	2	1
1	64	2	6	7.35	1.3	2.4	131	1.6	0	0	0	2	1
1	70	10	7	7.29	1.9	2.6	138	1.3	0	0	0	1	1
1	83	11	6	7.3	1.9	1.7	132	2.2	0	0	0	1	1
0	86	8	8	7.31	3.8	1.5	294	1.6	0	0	0	1	1
1	88	7	8	7.33	1.6	1.4	108	2.1	0	0	0	1	1
1	73	11	6	7.32	1.9	2.3	141	2.4	0	0	0	2	1
1	77	11	7	7.21	2.1	1.5	121	2.6	0	0	0	2	1
1	60	11	5	7.34	2.9	1.9	133	1.6	0	0	0	1	1
1	57	0	9	7.14	3.4	2.9	104	1.3	0	0	0	1	1
1	73	3	6	7.3	1.2	1.6	134	2.1	0	0	0	1	1
0	70	0	12	7.3	3.2	3.4	129	1.3	0	0	0	0	0
1	70	4	9	7.21	1.6	1.5	216	1.8	0	0	0	1	1
1	73	2	7	7.35	2.1	1.4	169	1.4	0	0	0	1	1
1	70	8	3	7.22	1.8	1.4	92	1.9	0	0	0	1	1
1	70	8	10	7.3	1.7	3.5	72	1.3	0	0	0	1	1
1	75	7	3	7.25	2.9	1.7	184	1.3	0	0	0	2	1
1	76	3	6	7.23	2	1.6	138	1.3	0	0	0	1	1
1	57	2	13	7.09	8.6	1.8	189	1.9	0	0	0	1	1

1	63	13	6	7.36	2.1	1.1	138	1.7	0	0	0	1	1
1	69	6	10	7.21	4.1	1.5	192	1.2	0	0	0	1	1
1	70	13	11	6.96	10	2.6	199	1.1	0	0	0	1	1
1	69	6	7	7.11	3.3	1.5	186	1.2	0	0	0	4	1
1	40	3	17	7.08	12	1.2	194	0.7	0	0	0	1	1
1	53	5	10	7.23	4.8	3.6	216	1.6	1	4	1	1	1
1	67	5	15	7.19	2.1	2.9	211	0.9	0	0	0	1	1
1	40	5	8	7.01	11	2.9	305	0.8	1	4	1	1	1
1	67	7	4	7.23	5.7	2.7	210	1.4	1	4	5	3	1
1	50	9	10	7.21	5	4	111	0.3	1	5	2	2	1
1	53	11	14	6.9	11	2.4	228	1	0	0	0	1	1
1	77	6	6	7.23	3.8	1.4	134	0.8	0	0	0	1	2
1	63	6	15	7.23	2.9	1.8	136	0.2	0	0	0	1	1
1	60	6	12	7.25	3.2	1.6	225	1.3	1	4	3	1	2
1	55	2	10	7.18	4.5	1.5	202	1.8	0	0	0	1	2
1	53	4	10	7.26	3.2	1.8	167	0.6	0	0	0	1	1
1	60	5	8	7.18	4.3	2.6	206	0.3	1	4	3	1	2
1	65	12	10	7.21	4.9	1.7	212	0.8	0	0	0	1	1
1	60	10	9	7.19	6	1.9	231	0.7	0	0	0	1	1
1	53	6	14	7.11	4.3	2.1	186	0.3	0	0	0	1	2
1	67	11	10	7.18	6	1.8	307	2.2	0	0	0	1	1
1	82	3	10	7.23	4.1	4.2	191	0.9	1	4	3	1	1
1	47	15	12	7.13	3	3.1	218	0.4	1	4	4	2	1
1	0	2	11	7.22	3.5	2.3	74	0.7	0	0	0	1	1
1	102	0	8	7.3	1.7	1.4	163	0.6	0	0	0	1	1
1	47	12	11	7.14	7.6	1.9	151	0.6	0	0	0	1	1
1	55	7	16	7.05	7.9	1.8	160	0.3	1	5	1	1	1
1	70	2	10	7.26	2.2	2.5	222	0.5	0	0	0	0	0
1	67	4	13	7.16	5.4	1.7	83	0.3	0	0	0	0	0
1	50	4	10	7.16	4.9	2.9	294	0.7	0	0	0	1	2
1	87	7	7	7.15	2.3	1.4	190	1.4	0	0	0	1	1
1	57	13	11	7	6.3	3.6	279	0.3	1	4	10	1	1
1	47	15	8	7.26	3	3.5	220	0.5	0	0	0	2	1
1	63	3	12	7.08	12	2.2	283	0.4	0	0	0	2	1
1	50	11	9	7.2	3	2.3	206	1.1	0	0	0	1	1
1	37	3	15	7.14	4.1	7.7	171	0.2	1	4	2	1	1
1	50	1	15	7.14	3.9	4.1	212	0.5	0	0	0	1	1
1	53	0	11	7.17	6.9	2.7	108	0.7	0	0	0	2	1
1	53	12	7	7.21	4.3	4.8	110	0.3	1	4	4	2	1
1	73	1	12	7.21	3.3	2.2	209	0.1	0	0	0	1	1
1	61	2	8	7.25	3.9	1.6	188	0.8	0	0	0	1	1
1	63	6	8	7.21	4.3	2.2	128	1.2	0	0	0	1	1
1	82	11	7	7.25	3.8	2.2	183	0.4	1	4	8	1	1
1	47	15	8	6.94	12	1.9	236	0.8	0	0	0	1	1
1	63	11	6	7.21	4.1	2	191	1.1	0	0	0	2	1
1	49	3	9	7.16	12	2	173	0.2	0	0	0	1	1
1	73	9	10	7.31	2.1	1.3	104	1.6	0	0	0	1	1